CK 05/82/01

NCI/ICRDB/CK05 82/01

PB82-935401

ICRDB CANCERGRAM

HORMONAL CARCINOGENESIS

SERIES CK05 No. 82/01

JANUARY, 1982

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In this issue:

- **ORAL CONTRACEPTIVES AND HUMAN CANCER** 1-4
- **ORAL CONTRACEPTIVES AND HUMAN HEPATIC ADENOMA** 5-6
- **ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER** 7
- **MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES** 8
- **MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES** 9
- **HORMONAL CARCINOGENESIS IN ANIMALS** 10-16
- **REVIEWS AND OTHER RELATED STUDIES** 17-34

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

ORAL CONTRACEPTIVES AND HUMAN CANCER

1. A CASE-CONTROL STUDY OF THE POSSIBLE ASSOCIATION BETWEEN ORAL CONTRACEPTIVES AND MALIGNANT MELANOMA.

Adam SA, Sheaves JK, Wright NH, Mosser G, Harris RW, Vessey MP

Dept. Community Medicine and General Practice, Univ. Oxford, Oxford, England

Br J Cancer; 44(1):45-50 1981

In a case-control study, we investigated 169 women aged 15-49 yr with malignant melanoma brought to the attention of the Oxford and South Western cancer registries during the yr 1971-76, together with 507 matched controls. Data about medical, reproductive, drug and smoking histories were obtained both by reviewing general practitioner (GP) records and from the women themselves by postal questionnaires. There was no significant evidence of any overall increase in the risk of melanoma in oral contraceptive (OC) users (data from GP records ever use vs never use, relative risk (RR) 1.34, 95% confidence limits 0.92-1.96; corresponding data from postal questionnaires - RR 1.13, limits 0.73-1.75). However, although not significant, the risk estimated from data in the postal questionnaires was higher in women who had used OCs for 5 yr or more (use greater than or equal to 5 yr vs never use, RR 1.57, limits 0.83-3.03). Previously demonstrated risk factors for melanoma, such as fair skin, blonde or red hair and Celtic origin were found to be commoner in the cases than in the controls. Data from the Oxford/Family Planning Association contraceptive study were also examined. Unexpectedly there was a strong suggestion of a negative association between OC use and melanoma risk, but the analysis was based on only 12 women with the disease. (Author abstract) (19 Refs)

2. BREAST CANCER, PREGNANCY, AND THE PILL.

Drife JO

Univ. Dept. Obstetrics and Gynaecology, Bristol Maternity Hosp., Bristol BS2 8EG, England

Br Med J; 283(6294):778-779 1981

Roles of parity and oral contraceptive use in the etiology of breast cancer are discussed. Clear histological and physiological changes are observed in the breast following pregnancy. A decrease in number of clear cells and an altered response to hormones is seen after a single pregnancy. Cyclic DNA and IgA synthesis are found only in parous women. Plasma concentrations of estrogen and progesterone are similar in both parous and nulliparous women, but pregnancy permanently alters the hormonal responsiveness of breast epithelium. The carcinogenic effect of estrogen unopposed by progesterone on the breast is hypothesized. Prior to pregnancy a woman has an inadequate number of endogenous progesterone receptors so that even with a combined estrogen-progesterone contraceptive pill, breast tissue may in effect experience 'unopposed' estrogen. Nulliparity and delayed first pregnancy may be important risk factors for subsequent breast cancer. Future study should focus not on hormonal profile but on effects of hormones on the breast itself. (24 Refs)

3. TRENDS IN THE INCIDENCE OF ENDOMETRIOID AND CLEAR CELL CANCERS OF THE OVARY IN THE UNITED STATES.

Cramer DW, Devesa SS, Welch WR

Dept. Obstetrics and Gynecology, Brigham and Women's Hosp., Boston, MA, 02115

Am J Epidemiol; 114(2):201-208 1981

An increase in the reported incidence of endometrioid and clear cell cancers of the ovary occurred in the United States during the 1970s, while no change occurred in the overall incidence of ovarian cancer. The authors cannot rule out that this was due to a shift in the criteria for histologic classification or improved coding, although there seem unlikely to account entirely for the change . In the four areas where the trend for endometrioid and clear cell cancers of the ovary was examined, the percent increases in their occurrence were correlated with the percent increases in the occurrence of carcinoma of the uterine corpus. The concomitant trends and the biologic similarities between these histologic types of ovarian cancer and the uterine cancers suggest that common etiologic factors may be involved. The role of postmenopausal estrogen use in the etiology of ovarian cancer must be clarified by further epidemiologic studies, but such studies should take tumor histology into consideration. (Author abstract) (18 Refs)

4. PROTECTIVE EFFECT OF ORAL CONTRACEPTIVES AGAINST CANCER OF THE REPRODUCTIVE ORGANS.

Johansson ED, Svanstrom L

Kvinnokliniken, Akademiska sjukhuset, Uppsala, Sweden

Lakartidningen; 78(28/29):2591-2592 1981

Studies on the protective effect of oral contraceptives, especially combined contraceptives, against cancer in the reproductive organs are reviewed. The combined oral contraceptives are more or less gestagen-dominated. They can therefore be expected to reduce the frequency of estrogen-dependent tumors. There is no clear evidence of a reduced incidence of breast cancer among women using such combined oral contraceptives: most studies show no change in the frequency of breast cancer, but one study showed reduced breast cancer risk in the age group 31-40 yr, and increased breast cancer risk in women who continued taking oral contraceptives beyond the age of 45 yr. Some studies showed a lower growth and later metastasized breast cancer in women who had used oral contraceptives compared with women who had not used contraceptives. The epidemiological studies show a marked reduction of the frequency of ovarian and endometrial cancer in women who had used oral contraceptives to half to one third of the frequency in women who had not used oral contraceptives. (12 Refs) (In SWE)

ORAL CONTRACEPTIVES AND HUMAN HEPATIC ADENOMA

5. POSSIBLE ASSOCIATION OF ANGIOSARCOMA WITH ORAL CONTRACEPTIVE AGENTS.

Shi EC, Fischer A, Crouch R, Ham JM
(c/o Ham) Dept. Surgery, Prince Wales Hosp., Randwick, New South Wales 2031, Australia
Med J Aust; 1(9):473-474 1981

Angiosarcoma of the liver has been reported to be associated with the long-term use of androgenic-anabolic and estrogenic steroids. It has been suggested that this tumor might develop in women after long-term exposure to oral contraceptive steroids, although this association has not yet been reported. We present here the clinical and pathological findings in a 42-yr-old woman who died of hepatic angiosarcoma after taking oral contraceptive steroids for 10 yr. (Author abstract) (13 Refs)

6. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.

Mettlin C, Natarajan N
Cancer Control and Epidemiology, Rosewell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 18(1):73-85 1981

Studies involving the role of oral contraceptive use in the etiology of benign and malignant liver tumors are reviewed. The evidence from these studies strongly suggests that there is a relationship between the use of oral contraceptives and benign liver tumors. The actual risk appears related to duration of usage and may also be related to the type of contraceptive steroid used. Further investigation is required to determine the oncogenic potential of oral contraceptives and the malignant potential of benign tumors. (Author abstract) (62 Refs)

ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER

7. BREAST CANCER INCIDENCE IN WOMEN WITH A HISTORY OF PROGESTERONE DEFICIENCY.

Cowan LD, Gordis L, Tonascia JA, Seegar Jones G
Lipid Res. Clinic, Population Studies, Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
Am J Epidemiol; 114(2):209-217 1981

In order to investigate the nature of the association of involuntarily delayed first birth and risk of breast cancer, 1,083 white women who had been evaluated and treated for infertility from 1945-1965 were followed prospectively through April 1978 to ascertain their breast cancer incidence. These women were categorized as to the cause of infertility into two groups, those with endogenous progesterone deficiency (PD) and those with nonhormonal causes (NH). Women in the PD group had 5.4x the risk of premenopausal breast cancer compared to women in the NH group. This excess risk could not be explained by differences between the two groups in ages at menarche or menopause, history of oral contraceptive use, history of benign breast disease or age at first birth. Women in the PD group also experienced a 10-fold increase in deaths from all malignant neoplasms compared to the NH group. The incidence of postmenopausal breast cancer did not differ significantly between the two groups. (Author abstract) (23 Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES

8. EFFECTS OF HEXESTROL, MEDROXYPROGESTERONE ACETATE AND CHLORMADINONE ACETATE ON 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED RAT MAMMARY CANCER IN RELATION TO ESTROGEN RECEPTOR.

Tominaga T, Kitamura M, Saito T, Itoh I
Dept. Surgery, Tokyo Metropolitan Komagome Hosp., Honkomagome 3-18-22, Bunkyo-ku, Tokyo 113, Japan
Gan; 72(4):604-609 1981

The effects of hexestrol (HXS), medroxyprogesterone acetate (MAP) and chlormadinone acetate (CMA) on 7,12-dimethylbenz[a]anthracene-induced mammary cancer in rats were evaluated. As a result of successive im injections of HXS at dosages of 2 or 10 mg/kg or MAP at dosages of 24 or 120 mg/kg, tumors were markedly reduced in size in all groups on day 7-day 14. These effects were the same regardless of the presence or absence of cytoplasmic estrogen receptors (ER) in tumors as determined by the dextran-coated charcoal method. Although such an effect was also seen with CMA, it was much less marked than the effects seen with HXS and MAP. The body wt of HXS-administered groups decreased considerably, whereas those of MAP-administered groups increased. These results may suggest that there is another endocrinological tumor-suppressing mechanism besides the mechanism involving the estrogen-ER system in large-dose administration of HXS and MAP. (Author abstract) (13 Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES

9. EFFECT OF PRETREATMENT WITH PREGNENOLONE-16ALPHA-CARBONITRILE AND PROTEIN-FREE DIET ON THE METABOLISM AND CARCINOGENICITY OF DIMETHYLNITROSAMINE.

Kiessling M, Lipinski R, Bohm N, Kleihues P
Pathologische Institut, Universitat Freiburg, 78 Freiburg, W. Germany
Carcinogenesis; 2(8):757-761 1981

Adult female Wistar rats were pretreated with a protein-free diet (PFD), pregnenolone-16alpha-carbonitrile (PCN: total dose 25 mg, 5 equal doses at 12-hr intervals), or a combination of both. Rats from each group were given a single injection of 60 mg dimethylnitrosamine (DMN). PCN-pretreated rats showed a 50% tumor incidence after a mean survival time of 672 days. PFD (30 rats) and PFD + PCN (28 rats) groups showed a tumor incidence of 83-85% and a mean survival time of 357 and 396 days. Rats treated only with PCN showed a tumor incidence of 50% with a mean survival time of 805 days. The incidence of neoplasms, particularly cholangiomas, was highest following treatment with PCN only. The PFD and PFD + PCN groups showed lower incidence of cystic cholangiomas and no malignant liver tumors. Methylation of liver DNA purines by a single dose of [14C] DMN was greatest in the PCN and PFD groups and lower in the PFD + PCN group. Methylation of renal DNA was highest in the PFD and PFD + PCN groups and lower in the PCN-only pretreated group. Differences in lung tissue were smaller among the various groups. Both PCN and PFD reduced the hepatotoxicity of DMN. PCN had no effect on the induction of renal tumors. Apparently PCN does not cause a reduction in DNM metabolism in the liver and the resultant increase in DNA methylation in the kidney. PFD shifts the metabolism of DMN from the liver to the kidney, lowering the carcinogenic effect of DMN in the liver and raising it in the kidney. (24 Refs)

HORMONAL CARCINOGENESIS IN ANIMALS

10. INFLUENCE OF THE ESTROUS CYCLE DURING CARCINOGEN EXPOSURE ON NITROSOMETHYLUREA-INDUCED RAT MAMMARY CARCINOMA.

Lindsey WF, Das Gupta TK, Beattie CW
(c/o Beattle) Div. Surgical Oncology, Univ. Illinois Medical Center, 840 South Wood St., Chicago, IL, 60612
Cancer Res; 41(10):3857-3862 1981

The influence of individual stages of the rat estrous cycle during exposure to l-nitroso-l-methylurea (NMU) on mammary tumor incidence, latency, number, and cytosol receptor dynamics for estrogen and progesterone was determined. Virgin female Buffalo rats were separated into three groups on day 53 according to their vaginal smear pattern. NMU (5 mg/100 g body wt, iv) was administered in 3 mo doses beginning at 53 to 55 days of age on diestrus, proestrus, or estrus between 9:00 and 11:00 a.m. Groups of rats had their second and third injections of NMU on the same day of the estrous cycle as their initial injection. All animals were killed during the morning on a diestrus day. Receptors for estrogen and progesterone were determined by a modified dextran-coated charcoal method and by sucrose density gradient analysis. Mean latencies to first tumor appearance in diestrus, proestrus, and estrus groups were 104.4, 83.6, and 91.4 days, respectively (p less than 0.05, diestrus versus estrus and proestrus) following the NMU injection. The mean number of tumors per rat was significantly higher in rats injected on proestrus (4.5) or estrus (4.3) than on diestrus (2.0). Estradiol bound to receptor sedimented at 8 and 4 s and was suppressed by diethylstilbestrol and estradiol. Progesterone receptor migrated to 7.8 and 4 s regions. Estrogen receptor incidence (100%) and content (16.7 fmol/mg cytosol protein) was highest in rats injected on diestrus. In the proestrus and estrus injected groups, estrogen receptor incidence was 95 and 63% and content was 10.2 and 11.2 fmol/mg protein, respectively. The affinity of estradiol for its receptor was not significantly altered in any group. Although there were no statistically significant differences in progesterone receptor incidence or affinity between groups, progesterone receptor content (74.6 fmol/mg cytosol protein) was significantly higher in tumors from rats injected on proestrus than on diestrus. These data suggest that the prevailing hormonal milieu of the estrous cycle during NMU exposure may be critically important to the subsequent biological behavior and steroid receptor status of carcinogen-induced rat mammary tumors. (Author abstract) (41 Refs)

11. HEPATOCELLULAR CARCINOMA INDUCED BY ESTROGEN AND PROGESTOGEN: DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN RATS FOLLOWING ORAL ADMINISTRATION OF SYNTHETIC ESTROGEN AND PROGESTOGEN.

Higashi S
First Dept. Surgery, Mie Univ. Sch. Medicine, Tsu, Japan
Mie Med J; 30(3):295-303 1981

Female Wistar rats were given daily 0.075 mg of ethinyl-estradiol (EES) and 6 mg of norethindrone acetate (NEA) dissolved in olive oil by gavage for 1 yr, another group received similar treatment for 18 mo, and a third group received olive oil alone for 1 yr and served as controls for the first group. In rats treated with EES and NEA, the liver wt increased markedly, while the body wt decreased. In the rats treated for 18 mo, the activities of glutamine oxaloacetic transaminase, glutamic pyruvic transaminase, and lactic dehydrogenase were higher and total cholesterol and triglyceride were lower, than those treated for only 1 yr. Multiple nodules ranging from 0.2 mm to 1 mm in diameter were observed in all the treated rats. These were hyperplastic nodules with compression and atrophy of the surrounding liver parenchyma. One of the 18 rats in the first group had a large, 2.5 x 2.0 x 1.5 cm, well-differentiated hepatocellular carcinoma composed of trabeculae of neoplastic cells. In rats treated for 18 mo, the number of hyperplastic nodules was higher and their size was larger than animals treated for 12 mo. These results support the hypothesis that EES and NEA may be initiators in hepatocarcinogenesis. (30 Refs)

12. OSSEOUS CHANGES AND OSTEOSARCOMAS IN MICE CONTINUOUSLY FED DIETS CONTAINING DIETHYLSTILBESTROL OR 17BETA-ESTRADIOL.

Highman B, Roth SI, Greenman DL
Div. Pathology Services, Natl. Center for Toxicological Res., Jefferson, AR, 72079
JNCI; 67(3):653-662 1981

In a study on the long-term effects of dietary diethylstilbestrol or 17beta-estradiol on C3H mice, estrogens induced a proliferation of osseous trabeculae and increased the incidence and hastened the development of osteofibrotic areas in the sterna. There were 6 osteosarcomas, 2 having metastases, in 1,242 mice fed dietary estrogens over 360 days, but none in 356 untreated controls. These tumors were reviewed along with 4 early sternal osteosarcomas selected from 17 osteosarcomas only 1 in a control found thus far in two other ongoing case comparable studies. In at least one and possibly in two other early cases, tumors were associated with areas of osteofibrosis, and one tumor was probably associated with proliferation of bony trabeculae in the medullary cavity. (Author abstract) (21 Refs)

13. EFFECT OF OVARIECTOMY ON SERIALLY TRANSPLANTED RAT MAMMARY TUMORS INDUCED BY 7,12-DIMETHYLBENZ[A]ANTHRACENE.

Lee C, Lapin V, Oyasu R, Battifora H
Dept. Urology and Cancer Center, Northwestern Univ. Medical Sch., Chicago, IL, 60611
Eur J Cancer Clin Oncol; 17(7):801-808 120 81

Mammary tumors in inbred Fischer 344 female rats were induced by 7,12-dimethylbenz[a]anthracene (DMBA). Primary tumors were excised and transplanted sc to syngeneic recipients. The transplanted tumors, thus developed, were used for further serial transplantation of up to five passages. Transplanted Tumors were able to grow to 1.5-2 cm in diameter within 1-2 mo. Histologically, tumor tissues of early passages were characterized by mixed populations of epithelial and spindle cells while tumors of late passages contained only the spindle cells. Tumors grafted into ovariectomized hosts were not able to grow, although they remained viable, since estrogen therapy was able to activate their growth. By the third passage, tumors were able to grow when transplanted into ovariectomized recipients but the growth rate was considerably slower than that in the intact hosts. In the fourth and fifth passages, tumors transplanted in ovariectomized recipients grew as well as those in intact hosts. Following the establishment of the transplanted tumors, ovariectomy in the hosts resulted in an initial regression and subsequent regrowth of tumors of early passages and had no effect on those of late passages. The long-term growth of transplanted tumors in ovariectomized hosts was associated with an increase in the spindle cell population which gradually replaced the regressed epithelial cells. Results suggest that the so-called 'hormone-dependent' DMBA-induced mammary tumors consist of at least two histologically and biochemically distinct cell types, hormone-dependent epithelial and hormone-independent spindle-shaped cells, and that the latter are selected over the epithelial component during serial transplantations or under unfavorable hormonal conditions due to ovariectomy in the hosts. (26 Refs)

14. HORMONAL INDUCTION OF KIDNEY TUMOURS IN MALE HAMSTERS. INHIBITION OF GROWTH BY A PHENOTHIAZINE DERIVATIVE (PERPHENAZINE).

Saluja PG, Hamilton JM, Thody AJ
Dept. Anatomy, Sch. Medicine, Aberdeen, Scotland
Eur J Cancer Clin Oncol; 17(7):767-773 1981

Experiments have shown that long-term treatment of male hamsters with estrogen will cause renal carcinomas, neoplastic changes in the pars intermedia of the pituitary and highly elevated levels of melanocyte-stimulating hormone (MSH). To test if MSH was fundamentally involved in renal carcinogenesis, a group of hamsters was treated for 317 days with perphenazine which is known to elevate MSH levels. A second group was treated with estrogen while a third received a combination of estrogen and perphenazine for a similar period of time. Serum MSH levels were significantly elevated in the perphenazine group but kidney tumors were absent. All estrogen-treated animals developed kidney tumors but only 19% of those given the combined treatment developed kidney tumors despite highly elevated levels of MSH. The findings suggest that MSH does not play a significant role in renal carcinogenesis in the hamster. Perphenazine may inhibit the induction of estrogen-induced tumors by competing with estrogen for receptors in the kidney or may protect cells from toxic injury by stabilizing cell and microsomal membranes. The phenothiazines are known to induce, and increase the activity of, microsomal enzymes and that may lead to enhanced detoxification of the carcinogen. Other effects of phenothiazines include elevation of prolactin levels. The fact that the body wt of animals treated with DES and perphenazine was significantly lower than that o f the other groups may indicate that the reduction in tumor incidence was the result of a certain degree of undernutrition. Further work is required to elucidate the mechanism of tumor inhibition by phenothiazine derivatives. (Author abstract) (32 Refs)

15. CONTRIBUTION OF THE STUDY OF EXPERIMENTAL CANINE GASTRIC CARCINOMA TO THE STUDY OF HUMAN GASTRIC CARCINOMA.

Kurihara M, Izumi T, Shirakabe H, Okui K, Miyazaka K, Maruyama S, Sasaki Y, Inaguma H, Kamano Y, Yasui A, Suwa B
Third Dept. Internal Medicine, Saitama Medical Sch., Saitama 350-04, Japan
I To Cho; 16(7):737-744 1981

Induction of experimental gastric carcinoma in dogs by N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) soln was investigated, and the dynamics of 5-fluorouracil (5FU) and uracil + 5-fluoro-1-(tetrahydro-2-furyl)-uracil (UFT) were studied in dogs bearing cancers. Gastric carcinomas were induced easily in the dogs by administering ENNG po 2x/day (13.8-23.8 g total) with food pellets, but scirrhous type gastric carcinoma was rarely induced with ENNG alone. On the other hand, 3/10 beagles given ENNG and gastrin developed scirrhous type carcinoma; all three tumors were observed in the pyloric and antrum regions of the stomach and were poorly differentiated adenocarcinomas. Signet ring cell carcinoma in the submucosa and marked proliferation of collagen fibers in the antrum were also observed. After iv injection and po administration of 14C-5FU to the ENNG-induced tumor-bearing dogs, higher concentrations of 5FU were observed in the cancer tissues (both superficial and deep) than in the normal tissues. Similar tests of UFT in a dog with ENNG-induced gastric carcinoma showed that 5FU concentrations were higher in the stomach and lungs than other tissues. (25 Refs) (In JPN)

16. ASSOCIATION OF ENDOMETRIAL TUMORS WITH REPRODUCTIVE TRACT ABNORMALITIES IN THE AGED RAT.

Tang FY, Tang LK
Dept. Obstetrics, Biochemistry,, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14642
Gynecol Oncol; 12(1):51-63 1981

The incidence of spontaneous tumors of the endometrium in Fischer 344 rats increases with age to a max of 55% at 32 mo ($n = 22/40$). The incidence of tumors was associated with an altered endocrine status in these aged rats. Forty-five percent of these endometrial lesions are associated with the presence of ovarian cysts. Vaginal cytology in all of the 31-mo-old rats bearing uterine tumors exhibited an acyclic or anestrus pattern. Serum levels of estradiol, testosterone, and LH were lower, whereas those of prolactin were higher in these aged rats than those of young rats. Pituitary cultures derived from the 31-mo-old animals exhibited an absence of estrogen-stimulated LH release which was present in cultures derived from cycling 9-mo-old Fischer rats. The data indicate a correlation between an anovulatory, acyclic reproductive pattern and etiology of these endometrial tumors. The aged Fischer rat may thus provide an animal model for the study of the hormonal etiology of this class of tumors. (Author abstract) (8 Refs)

REVIEWS AND OTHER RELATED STUDIES

17. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.

Eveson JW
Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(3):129-146 1981

Since the oral mucosa is more resistant to the actions of chemical carcinogens than skin, early attempts to produce experimental malignant oral tumors were largely unsuccessful. The induction of squamous cell carcinomas in the thin lining mucosa of the hamster cheek pouch is discussed in detail, including the standardization the model, metastases, solvents, electron microscopy, histochemistry, cell kinetics, co-carcinogenesis, nutritional status, and hormones. Problems associated with this model of carcinogenesis include the debate about whether the tissue is truly intraoral, that the cheek pouch is a site of immunological privilege, and the tissue is technically difficult to handle. Models of intra-oral carcinogenesis in extrapouch sites include those using hamsters, mice, rats, and primates. The resistance of the oral mucosa to chemical carcinogens is discussed. At this time, the most suitable models of oral carcinogenesis are the hamster cheek pouch and tongue models using 9,10-dimethyl-1,2-benzanthracene and the rat palate model using 4-nitroquinoline N-oxide. (136 Refs)

18. BIOLOGIC MARKERS IN CANCER DIAGNOSIS AND TREATMENT.

Holyoke ED, Block GE, Jensen E, Sizemore GW, Heath H, Chu TM, Murphy GP, Mittelman A, Ruddon RW, Arnott MS
Roswell Park Memorial Inst., Buffalo, NY
Curr Probl Cancer; 6(2):68pp. 1981

The clinical use of tumor markers in detecting and monitoring the progress of tumor treatment is reviewed. In breast cancer treatment, the intracellular presence of an estrogen receptor protein identifies those tumors that are hormone-dependent and thus capable of responding to hormone manipulation (therapy). The presence or absence of progesterone receptors has not proved clinically useful. Calcitonin has been shown to be useful as a biological marker of medullary thyroid carcinoma; there are numerous tests and measurements for it, such as pentagastrin injection, long calcium infusion, short calcium infusion, and ethanol ingestion. The measurement of elevated levels of prostatic acid phosphatase by such techniques as radioimmunoassay, counterimmunoelectrophoresis, solid-phase immunofluoroassay, and solid-phase immunoadsorbent assay offers a method of identifying patients in the early stages of prostate cancer and monitoring the efficacy of treatment. The detection of certain 'tumor-associated antigens' such as alpha-fetoprotein, tissue peptide antigen, fetosulfoglycoprotein, pancreatic oncofetal antigen, and carcinoembryonic antigen (CEA) have various applications in screening, diagnosis, and staging of cancer; CEA may be of value in monitoring the adequacy of therapy and the treatment of advanced disease and in detecting persistent progressive disease in patients with colon cancer; alpha-fetoprotein is sensitive and specific enough for hepatocellular cancer to be of clinical use in this disease. Various protein degradation products are associated with tumors; plasminogen-dependent protease activity is one of the most likely candidates for a proteolytic activity as a tumor marker substance. Measurements of plasminogen activator, plasmin-derived products, and plasma protein degradation products in serum and/or urine are being investigated for their utility as tumor markers. Measurements of tissue aryl hydrocarbon hydroxylase may help to identify populations at risk of cancer resulting from chemical carcinogenesis. (245 Refs)

19. VISUALIZATION BY LIGHT AND SCANNING ELECTRON MICROSCOPY OF REPRODUCTIVE TRACT LESIONS IN FEMALE MICE TREATED TRANSPLACENTALLY WITH DIETHYLSTILBESTROL.

Lamb JC, Newbold RR, McLachlan JA

Natl. Toxicology Program, P. O. Box 12233, Research Triangle Park, NC, 27709

Cancer Res; 41(10):4057-4062 1981

Pregnant female mice were exposed to diethylstilbestrol or 11beta-methoxy-17beta-estradiol on days 9 to 16 of gestation. The female offspring of these animals were then examined for reproductive tract abnormalities. Scanning electron microscopic and histological evaluation of these specimens demonstrated reproductive tract lesions in all treatment groups when compared to matched control mice. These lesions included displacement of the squamocolumnar junction, uterine squamous metaplasia, atypical uterine cell surface specializations, protrusions of uterine cells, vaginal and cervical papillary growths, enlarged uterine cervix, abnormal vaginal and uterine folding patterns, female hypospadias, and the presence of vaginal concretions. Scanning electron microscopic observations proved particularly useful in studying lesions which involved the disruption of the normal structure and shape of the reproductive tract and the displacement of cell types. (Author abstract) (22 Refs)

20. THE EPIDEMIOLOGY AND PATHOGENESIS OF THE MAMMARY CANCER.

Pimentel E

Catedra de Fisiopatologia, Universidad Central de Venezuela, Caracas, Venezuela

Rev Fac Med Univ Cent Venez; 1(1):27-47 1981

The mammary cancer is five to six times more frequent in the northern countries of Europe and in North America, then in Asia and Africa. The southern European countries and South America are in between. This is a general rule with notable exceptions. In 1978 in Venezuela the total cancer mortality was 13.5%. The mammary cancer was 9.6% of the total women cancer mortality and it was in the fourth place. In the United States the mammary cancer was in the first place with 13.6% of the total women cancer mortality. The pathogenic factors are endogenous (genetic, immunologic, hormonal, reproductive, neural) or exogenous (diet, ionizing irradiation, chemical carcinogens, oncologic viruses). The relative importance of each factor is very variable from one species to another and there are notable differences between various stocks of the same species. The pathogenic factors of human mammary cancer are not well known. The genetic factors seem to be important in the minority of cases. The immunologic and hormonal factors probably are not involved in the transformation of the normal cells, but they influence the growth of neoplastic cells. There are no carcinogenic substances known, which play a role in the origin of the human mammary cancer. A minority of cases are related to ionizing irradiation. The possible role of virus is not yet elucidated. (63 Refs) (In SPA)

21. ENDOGENOUS CARCINOGENS.

Hill MJ
Bacterial Metabolism Res. Lab., Central Public Health Lab., London, England
Practitioner; 225(1356):803-804,807-809 1981

Estradiol is a potential endogenous carcinogen. Consuming a high fat/high energy diet, by increasing circulating estrogen levels and estrogen receptor activity, may increase the risk of carcinogenesis in estrogen-dependent tissues (breast, endometrium, possibly ovary). The role of of cholesterol in carcinogenesis is not yet clear. The author's studies showed no relationship between fecal cholesterol levels and the risk of intestinal cancer in case-control studies. Some of the numerous urinary metabolites of tryptophan seem to be related to non-industrial bladder cancer. Intestinal bacteria can derive carcinogenic substances (ethionine, phenol, p-cresol, N-nitroso compounds, bile acid metabolites, etc) from dietary components and convert exogenous chemicals (eg, polycyclic aromatic hydrocarbons) to proximate carcinogens. It is relatively easy to determine which carcinogens might be produced under ideal conditions, but there is limited information on which carcinogens are actually produced in vivo, and very little information regarding their importance. (27 Refs)

22. SOME RISK FACTORS OF BREAST CANCER.

Scolozzi R, Salmi R, Coccafogli A, Dell'Acqua G
Istituto di Clinical Medica Generale e Terapia Medica, Universita, Ferrara, Italy
Recenti Prog Med; 70(5):463-486 1981

Studies on the risk factors of breast cancer are reviewed. High stature, overweight (obesity), early menarche, hyperestrogenic, reduced fertility, advanced age at first childbirth, short overall duration of lactation, high-caloric, high-fat diet, long-term use of oral contraceptives, especially before the first pregnancy, late menopause, and exposure to ionizing radiation, especially during and shortly after puberty are generally recognized risk factors along with family history of breast cancer. The long-term use of hair dyes, especially of permanent ones, is also considered a risk factor for breast cancer along with other cancers. (134 Refs) (In ITA)

23. GLUCOCORTICOIDS AND BENZO(A)PYRENE HAVE OPPOSING EFFECTS ON EGF RECEPTOR BINDING.

Ivanovic V, Weinstein IB
Div. Environmental Sciences and Cancer Center/Inst., Cancer Res. Columbia Univ., Coll. Physicians and Surgeons, 701 West 168th St., New York, NY, 10032
Nature; 293(5831):404-406 1981

Epidermal growth factor (EGF)-receptor binding was used as a marker for membrane effects in C3H10T1/2 mouse embryo fibroblasts exposed to the potent glucocorticoid fluocinolone acetonide (FA), and to the carcinogens benzo(a)pyrene (BP), and 12-O-tetradecanoyl-phorbol-13-acetate (TPA). FA alone produced a 1.9x stimulation of EGF-receptor binding over that observed in control cultures. The stimulation was apparent within 1 hr and reached a max by 24 hr. FA pretreatment (2 x 10(-7) M) protected the cells from the approx 50% inhibition of EGF-binding induced by BP (2 x 10(-6) M) or TPA (10(-9) M). Results suggested that glucocorticoids inhibit carcinogenesis by inducing cell membrane changes that are reciprocal to those induced by carcinogens and tumor promotors. (22 Refs)

24. THE INFLUENCE OF GESTAGEN-ORIENTED ORAL CONTRACEPTIVES ON THE MILK DUCT EPITHELIUM - CYTOLOGICAL FINDINGS IN MAMMARY SECRETIONS.

Wunderlich M
Gynakologisch-Geburtshilfliche Klinik, Kreiskrankenhauses Altenburg, 7400 Altenburg, E. Germany
Dtsch Gesundheitswes; 36(27):1139-1141 1981

The general influence of oral contraceptives on breast parenchyma and their ability to stimulate pathophysiological secretion have been repeatedly described; yet there are no investigations concerning specific preparations. On the basis of a number of our own patients we showed that especially after long-term ingestion of Nonovlon - a gestagen-oriented contraceptive - a conspicuous number of mild and moderate types of dysplasia of the cells of the mammary secretion could be found in cytological examinations. Without drawing any binding conclusions, these findings should stimulate further intensive research investigations in order to avoid probable dangerous side-effects after long-term administration of oral contraceptives. (Author abstract) (16 Refs) (In GER)

25. POSSIBILITIES AND PROBLEMS OF ORGAN-SELECTIVE AGENTS AND DRUGS.

Hamacher H
Konigin-Luise Str. 2-4, D-1000 Berlin, W. Germany
Pharmazie; 36(6):391-399 1981

The development of organ-selective methods of treatment are reviewed, and several specific types of treatment are described. Localized therapy involves the introduction of an agent into the site to be treated. An example of this is the progesterone intrauterine contraceptive system. A second method relies on the differences between metabolic processes in normal and malignant cells. Compounds such as cyclophosphamides are used to selectively poison tumor cells. Acid-stimulating compounds can lower the pH of tumor cells, allowing cytotoxic agent active at lower pH to be effective. Liposomes, in which water-soluble compounds are enveloped in lipid double-layers, enable the transport of agents selectively into target cells. Micelles work in a similar manner. Certain radioactive elements have been shown to accumulate selectively in certain organs, such as 131I in the thyroid. This has provided diagnostic and therapeutic tools, useful particularly in malignant diseases. The combining of isotopes with specific carrier compounds allows the specific targeting of organs or tissues. Hormones with specific organ affinities, as well as specific hormone receptors, can also be used to direct cytotoxic agents at specific targets. The development of organ-specific treatments has many possibilities for treatment of cancer and other diseases. (52 Refs) (In GER)

26. CURRENT STATUS OF THERAPEUTIC MODALITIES FOR TREATMENT OF GYNECOLOGIC MALIGNANCIES WITH EMPHASIS ON CHEMOTHERAPY.

Willson JK, Ozols RF, Lewis BJ, Young RC
(c/o Young) Medicine Branch, NCI, NIH, Bethesda, MD, 20205
Am J Obstet Gynecol; 141(1):81-98 1981

The current status of conventional therapies for gynecological malignancies is reviewed with special emphasis on the efficacy of chemotherapy. Detailed discussions are presented on the prognostic factors, surgical management, radiotherapy, chemotherapy, along with recommendations relative to ovarian cancer (including malignant germ cells tumors), carcinoma of the cervix, endometrial cancer and gestational trophoblastic disease. Radiotherapy in combination with surgery is the treatment of choice for malignant germ cell tumors of the ovary, carcinoma of the cervix, and low-risk Stage I endometrial cancer. The patients with advanced ovarian cancer, advanced carcinoma of the cervix who have para-aortic node metastases, advanced endometrial cancer, and uterine sarcoma who have an extrapelvic extension of the disease, high-grade histology, or metastases would benefit from aggressive postsurgical systemic therapy. Chemotherapy regimens containing bleomycin and mitomycin C were found to improve the survival of the patients with advanced cervical cancer. Progestational agents were used widely in the treatment of endometrial cancer: the efficacy of hormonal therapy was found to depend upon the progesterone affinity of the tumor. Drug regimens containing adriamycin and dacarbazine were the most effective in the patients with soft tissue uterine sarcomas. (199 Refs)

27. ENHANCED CYTOSTATIC EFFECTIVENESS OF ANILINE MUSTARD AGAINST 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED RAT MAMMARY TUMORS DURING REGRESSION IN RESPONSE TO OVARIECTOMY.

Benckhuysen C, Ter Hart HG, Van Dijk PJ
Dept. Biochemistry, Antoni Van Leeuwenhoek-Huis, Netherlands Cancer Inst., 121 Plesmanlaan, 1066 CX Amsterdam, The Netherlands
Cancer Treat Rep; 65(7/8):567-574 1981

Sprague-Dawley rates bearing 7,12-dimethylbenz[a]anthracene (DMBA)-induce mammary tumors were treated with either of two aromatic alkylating agents, aniline mustard or melphalan, alone or combined with ovariectomy. Both drugs were applied once a wk for 8 wk. Eighty-four percent of the tumors responded to ovariectomy, 38% regressing completely and 46% regressing partially. Aniline mustard, though virtually ineffective as a single agent, appeared synergistic with ovariectomy: a 100% regression rate (72% complete, 28% partial) was observed for this combination. Treatment with melphalan was as effective as ovariectomy, but the combination of melphalan with ovariectomy was no more effective than either treatment alone. The end product of aniline mustard metabolism, p-hydroxyaniline mustard O-glucuronide, may be more extensively activated by beta-glucuronidase in hormonally regressing than in growing or stationary tumors. Intratumoral levels of beta-glucuronidase occurring in DMBA-induced tumors 4 days after ovariectomy were found to be similar to those in the aniline mustard-sensitive mouse plasma cell tumor ADJ/PC6. It remains to be more extensively studied whether an effect of endocrine treatment on tumor beta-glucuronidase levels, and possibly on intracellular distribution of enzyme, could be used therapeutically. An effectively scheduled cytostatic treatment (with a drug conjugate such as that formed metabolically from aniline mustard) in conjunction with ovariectomy might be effective in the treatment of hormone-responsive breast cancer. (Author abstract) (29 Refs)

28. EFFECTS OF ESTROGEN TREATMENT ON HUMAN TESTICULAR UNCONJUGATED STEROID AND STEROID SULFATE PRODUCTION IN VIVO.

Leinonen P, Ruokonen A, Kontturi M, Vihko R
Dept. Clinical Chemistry, Univ. Oulu, SF-90220 Oulu 22, Finland
J Clin Endocrinol Metab; 53(3):569-573 1981

To analyze the relationships between human testicular unconjugated and sulfate-conjugated steroids, we investigated the effects of estradiol [polyestradiol phosphate (E2)] and a synthetic estrogen [diethylstilbestrol diphosphate (DESDP)] on testicular, spermatic venous, and peripheral venous serum concentrations of these compounds. Six unconjugated steroids and four steroid sulfates were measured by specific RIAs after chromatography in 27 prostatic carcinoma patients without preceding endocrine therapy and in 29 patients castrated after E2 or DESDP treatment. E2 treatment decreased testicular concentrations of pregnenolone, testosterone (T), and 5 alpha-dihydrostestosterone (DHT). Testicular Androstenedione concentrations were also decreased, whereas progesterone concentrations increased, and there were decreased testicular concentrations of dehydroepiandrosterone sulfate (DHEA-SO4) and 5-androstene-3beta,17beta-diol sulfate. Spermatic venous concentrations of 17alpha-hydroxyprogesterone (17-OHP), T, and DHT as well as those of DHEA-SO4 and T sulfate were decreased after E2 treatment, and in the case of T, DHEA-SO4, and 17-OHP, this change was also reflected in peripheral serum concentrations. In the doses used, DESDP treatment was clearly more efficient than E2, and it decreased testicular concentrations and the secretion of all unconjugated and sulfated steroids. However, the difference between the effects of E2 and DESDP on peripheral serum steroid concentrations was mainly limited to those most clearly of testicular origin (17-OHP, T, and DHT). These findings show that estrogen treatment has an inhibitory effect on human testicular steroid sulfate production in vivo in addition to the known depressing effect on unconjugated steroid production. The results from E2-treated patients suggest that the changes in steroid sulfates are secondary to those in unconjugated steroids. The most probable sites of inhibition are a step before pregnenolone and the enzymes 17alpha-hydroxylase and 17-20-desmolase in the biosynthetic chain leading to T synthesis. (Author abstract) (37 Refs)

29. NEW CONCEPTS IN NUTRITION AND CANCER: IMPLICATIONS FOR FOLIC ACID.

Butterworth CE
Dept. Nutrition Sciences, Univ. Alabama, Birmingham, AL, 35294
J Dent Child; 48(4):300-303 1981

Many of the proposed mechanisms by which diet and nutrition may be related to cancer seem to involve a genetic or chromosomal injury that may be conditioned by nutritional factors such as folic acid (FA). Hormone-induced localized nutrient deficiency has been postulated as a mechanism involved in the development of cervical dysplasia in women taking oral contraceptives (OCs). In a clinical trial, FA supplementation led to the regression of OC-induced cervical dysplasias in women who continued to take OCs. No such regression occurred in placebo-treated women, some of whom developed carcinoma in situ. The concept of nutritionally dependent fragile sites and somatic mutations on human chromosomes is not supported by clear evidence that chromosomal fragility is involved in carcinogenesis. However, a combination of chromosomal fragility and deficiencies of FA or another essential nutrient may account for specific mutations in target tissues. One published report describes 34 cases of serious hematologic disease (including 5 acute leukemias) in a family with an inherited defect of cellular FA uptake. Cervical cancer is circumstantially linked to a DNA virus (herpesvirus), and several RNA viruses are known to be oncogenic in animals. The retroviruses induce RNA-directed DNA synthesis via reverse transcriptase. There is good reason to suspect that FA-containing coenzymes play an important role in this DNA synthesis, as they do elsewhere. Folacin plays an important role in the infection of Escherichia coli by T-even bacteriophages. FA and its analogs may play a similar role in viral oncogenesis. (17 Refs)

30. PRENEOPLASTIC LESIONS OF THE MAMMARY GLAND. (ONCOLOGY OVERVIEW)

International Cancer Research Data Bank

ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205

Preneoplastic Lesions of the Mammary Gland (Oncology Overview) Medina, D, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923002; OB-81/02:134pp. 1981

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute. They are retrospective bibliographies containing 100-500 selected abstracts of published research on topics of high interest to cancer investigators. The scope of this Oncology Overview emphasizes the basic biological aspects of preneoplastic and pseudoneoplastic lesions of human, rodent, and canine mammary glands in vivo and in vitro. Induction and modulation of mammary preneoplasias by carcinogens, hormones and other agents, as well as hormonal responsiveness, immunologic aspects, cytogenetics, and angiogenesis studies are presented. Also of interest are metabolic, enzymatic, and histochemical evaluations of preneoplastic breast lesions. In studies of mammary preneoplasias in humans, ultrastructural and histopathological characteristics, radiologic evaluation, cytology of aspirations and secretions, and cytomorphometry are included. Risk estimates of malignant potential of these breast lesions are also considered. The Overview excludes studies purely concerned with the treatment and/or management of patients with breast preneoplasias.

31. INFLAMMATION AND TUMOR GROWTH. I. TUMOR GROWTH IN MICE WITH DEPRESSED CAPACITY TO MOUNT INFLAMMATORY RESPONSES: POSSIBLE ROLE OF MACROPHAGES.

Nelson M, Nelson DS, Hopper KE

Kolling Inst. Medical Res., Royal North Shore Hosp., St. Leonards NSW 2065, Australia

Am J Pathol; 104(2):114-124 1981

Studies were made of the effects of various treatments on the growth in mouse feet of isografts of two methylcholanthrene-induced fibrosarcomas: C-4, of CBA/J mice, and A-2, of A/J mice. The isografts were prepared by pronase digestion of sc tumors and were injected as unseparated cell suspensions or as tumor-cell-enriched suspensions after depletion of infiltrating host inflammatory cells. The recipient mice were untreated or treated with reserpine, sublethal whole body irradiation, cyclophosphamide, or corticosteroids. Depletion of host cells from the inoculum resulted in increased growth from the same number of tumor cells. Reserpine treatment decreased the growth of both tumors, whether unseparated or tumor-cell-enriched, and whether injected into the foot or the flank. Irradiation, cyclophosphamide pretreatment, and corticosteroid pretreatment decreased the growth of normal inocula or enriched inocula or both. The effects of cyclophosphamide and corticosteroids were apparently not due to cytotoxicity to tumor cells. Normal resident peritoneal cells increased tritiated thymidine uptake by tumor cells in vitro. Sedimentation velocity separation showed the largest cells to be the most potent. It is suggested that some host inflammatory reaction is necessary for optimal tumor growth and that murine hosts produce not only cells with antitumor effects but also cells, possibly a subpopulation of macrophages, that potentiate tumor growth. (Author abstract) (54 Refs)

32. 20-YEAR RESEARCH ON THE SUBJECT OF PREGNANCY ASSOCIATED ALPHA2-GLYCOPROTEIN - SIGNIFICANCE OF THE DETERMINATION OF THESE PROTEINS IN CLINICAL STUDY.

Bundschuh G
Institut fur Transfusiologie und Transplantologie des Bereichs Medizin, (Charite) Humboldt-Universitat zu Berlin, Tucholskystrasse 2, DDR-1040 Berlin, E. Germany
Dtsch Gesundheitswes; 36(28):1193-1199 1981

The range of variation of individual concentrations of pregnancy associated alpha2-glycoprotein (PAG) is not a normal distribution, but a multi-peaked distribution, which presumably is an expression of the genetic background. For this reason it is statistically inadmissible to use mean values for reference purposes. Some physiological or pathological processes have an anabolic influence on the PAG level. They include especially the action of estrogen, tumor growth, immune defects which are possibly manifested humorally, rheumatoid arthritis, hepatitis/diabetes combination. A correlation between predisposition to tumor formation and the PAG level cannot be established in this direct manner. It was determined through family examinations. Decreases in PAG levels after the removal of tumors and early increases in PAG levels in cases of relapse or formation of metastases can be used for case control of tumor risk groups. The other anabolic influences, which are known to date, must be ruled out. The use of PAG determinations as a tumor search test is advisable only when the individual, genetically determined initial values are known. The lowering of the PAG level immediately after the withdrawal of estrogenic contraceptives should be checked during the period without medication. (Author abstract) (66 Refs) (In GER)

33. INHIBITION OF CLONOGENIC GROWTH OF MELANOMA CELLS BY COMBINATION OF MELANOCYTE STIMULATING HORMONE AND THEOPHYLLINE.

Wick MM
Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
J Invest Dermatol; 77(3):253-255 1981

The combination of MSH and theophylline is synergistic in inhibiting the growth as well as stimulating the differentiation of pigmented melanoma cells. In order to determine if a permanent alteration in the proliferative potential of these cells was achieved, we examined the effect of MSH and theophylline alone and in combination upon the plating efficiency and tumorigenicity of S-91 Cloudman melanoma cells. Following treatment with the combination of MSH and theophylline, the cells became deeply pigmented and had their colony forming ability reduced to 28% of control. Neither MSH or theophylline alone, although effective in reducing the growth rate of the cells, caused a significant reduction in clonogenic growth. When cells were pretreated with MSH and theophylline alone or in combination and reinjected into mice, the combination of MSH and theophylline caused a significant reduction in percentage of animals developing tumor (reduced to 14% of control). Cells treated with either MSH or theophylline alone were similar in their tumorigenic potential to control cells. These effects were selective since the nonmelanocytic control cells, mouse fibroblast L929 and Chinese hamster ovary when treated similarly did not exhibit any alteration in their clonogenic potential. The treatment of responsive cells with the combination of MSH and theophylline is capable of causing permanent decrease in the proliferative potential of murine melanoma cells and may have relevance to the treatment of this disease in man. (Author abstract) (12 Refs)

34. OSTEONECROSIS IN PATIENTS WITH MALIGNANT LYMPHOMA: A REVIEW OF TWENTY-FIVE CASES.

Engel IA, Straus DJ, Lacher M, Lane J, Smith J
Dept. Radiology, Memorial Sloan-Kettering Cancer Center, 1375 York Ave., New York, NY, 10021
Cancer; 48(5):1245-1250 1981

A retrospective study of 25 patients with malignant lymphoma who had osteonecrosis of either the femoral or humeral head(s) was undertaken. The common factor present among all patients was the administration of intermittent steroid-containing combination chemotherapy. Seventeen Hodgkin's disease patients received chemotherapy predominantly consisting of an alkylating agent, vincristine, procarbazine, and moderate amounts of prednisone. The non-Hodgkin's lymphoma patients were on various moderate dosage steroid-containing protocols, except three who received prolonged high-dose steroid-containing chemotherapy regimens. Sixteen of the 17 Hodgkin's disease patients and five of the eight non-Hodgkin's lymphoma patients received radiotherapy to the bones that subsequently developed osteonecrosis. Two of the three non-Hodgkin's lymphoma patients who were not irradiated were treated with high-dose steroid-containing chemotherapy regimens. Symptoms developed in patients 12 mo and 32 mo after completion of chemotherapy and radiotherapy, respectively. Osteonecrosis was a long-term complication of treatment between 1970 and 1979 and occurred in 1.6% of the Hodgkin's disease and 0.12% of the non-Hodgkin's lymphoma patients treated. The authors conclude that the patients at highest risk for this complication are those who receive both radiotherapy to the affected bone(s) and intermittent steroid-containing multiple drug chemotherapy. (Author abstract) (24 Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Adam SA ... 1
Arnott MS ... 18
Battifora H ... 13
Beattie CW ... 10
Benckhuysen C ... 27
Block GE ... 18
Bohm N ... 9
Bundschuh G ... 32
Butterworth CE ... 29
Chu TM ... 18
Coccafogli A ... 22
Cowan LD ... 7
Cramer DW ... 3
Crouch R ... 5
Das Gupta TK ... 10
Dell'Acqua G ... 22
Devesa SS ... 3
Drife JO ... 2
Engel IA ... 34
Eveson JW ... 17
Fischer A ... 5
Gordis L ... 7
Greenman DL ... 12
Ham JM ... 5
Hamacher H ... 25
Hamilton JM ... 14
Harris RW ... 1
Heath H ... 18
Higashi S ... 11
Highman B ... 12
Hill MJ ... 21
Holyoke ED ... 18
Hopper KE ... 31
Inaguma H ... 15
International C ... 30
Itoh I ... 8
Ivanovic V ... 23
Izumi T ... 15
Jensen E ... 18
Johansson ED ... 4
Kamano Y ... 15
Kiessling M ... 9
Kitamura M ... 8
Kleihues P ... 9
Kontturi M ... 28
Kurihara M ... 15
Lacher M ... 34
Lamb JC ... 19
Lane J ... 34
Lapin V ... 13
Lee C ... 13
Leinonen P ... 28
Lewis BJ ... 26
Lindsey WF ... 10
Lipinski R ... 9
Maruyama S ... 15
McLachlan JA ... 19
Mettlin C ... 6
Mittelman A ... 18
Miyazaka K ... 15
Mosser G ... 1
Murphy GP ... 18
Natarajan N ... 6
Nelson DS ... 31
Nelson M ... 31
Newbold RR ... 19
Okui K ... 15
Oyasu R ... 13
Ozols RF ... 26
Pimentel E ... 20
Roth SI ... 12
Ruddon RW ... 18
Ruokonen A ... 28
Saito T ... 8
Salmi R ... 22
Saluja PG ... 14
Sasaki Y ... 15
Scolozzi R ... 22
Seegar Jones G ... 7
Sheaves JK ... 1
Shi EC ... 5
Shirakabe H ... 15
Sizemore GW ... 18
Smith J ... 34
Straus DJ ... 34
Suwa B ... 15
Svanstrom L ... 4
Tang FY ... 16
Tang LK ... 16
Ter Hart HG ... 27
Thody AJ ... 14
Tominaga T ... 8
Tonascia JA ... 7
Van Dijk PJ ... 27
Vessey MP ... 1
Vihko R ... 28
Weinstein IB ... 23
Welch WR ... 3
Wick MM ... 33
Willson JK ... 26
Wright NH ... 1
Wunderlich M ... 24
Yasui A ... 15
Young RC ... 26

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICOLOGICAL ASPECTS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH).

De Fernicola NA, De Azevedo FA
Divisao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
Rev Bras Saude Ocup; 33(9):62-68 1981
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2. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.

International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

3. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.

Mettlin C, Natarajan N
Cancer Control and Epidemiology, Rosewell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 18(1):73-85 1981

RADIATION CARCINOGENESIS

4. EXPERIMENTAL RADIATION CARCINOGENESIS: WHAT HAVE WE LEARNED?

Fry RJ
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Radiat Res; 87(2):224-239 1981

5. INFLUENCE OF NONCARCINOGENIC SECONDARY FACTORS ON RADIATION CARCINOGENESIS.

Little JB
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Radiat Res; 87(2):240-250 1981

6. MEDICAL IRRADIATION IN JAPAN - STOCHASTIC RISK ESTIMATION AND ITS REDUCTION.

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Div. Physics, National Inst. Radiological Sciences, 9-1 Anagawa 4-Chome, Chiba Shi 260, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(5):445-474 1981
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7. RADIOACTIVITY IN DRINKING WATER.

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Office of Drinking Water, Environmental Protection Agency, Washington, DC
Radioactivity in Drinking Water. Available from National Technical Information Service, Springfield, VA, as PB81-192833:, 79 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. EPIDEMIOLOGY OF GASTROINTESTINAL CANCER.

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9. EPIDEMIOLOGICAL ASPECTS OF ESOPHAGEAL CANCER.

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IV Cattedra di Clinica Chirurgica Generale e Terapia Chirurgica, Universita degli Studi di Roma, Rome, Italy
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10. PANCREATIC CANCER.

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11. GENETICALLY DETERMINED SUSCEPTIBILITY TO CANCER.

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Blood; 58(3):415-419 1981

12. ETIOLOGY, ROLE AND DETECTION OF CHROMOSOMAL ABERRATIONS IN MAN.

Fabricant JD, Legator MS
Dept. Preventive Medicine, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
JOM; 23(9):617-625 1981

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13. INDUSTRIAL CARCINOGENESIS.

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14. ENVIRONMENT AND HEALTH (LITERATURE REVIEW).

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Higginson J
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Institutul de igiena si sanatate publica, Iasi, Romania
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17. REVIEW OF UICC PROGRAM ON SMOKING AND LUNG CANCER.

Gray N
Smoking and Cancer Program, UICC, 3 rue du Conseil General, 1205 Geneva, Switzerland
Cancer Forum; 5(1):15-18 1981

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18. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.

Laishes BA
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
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Preneoplastic Lesions of the Mammary Gland (Oncology Overview) Medina, D, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923002; OB-81/02:134pp. 1981

21. LYMPHOCYTE DIFFERENTIATION: AN ESSENTIAL BASIS FOR THE COMPREHENSION OF LYMPHOID NEOPLASIA.

Magrath IT
Pediatric Oncology Branch, Div. Cancer Treatment, NCI, NIH, Public Health Service, United States Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(3):501-514 1981

MODIFICATION OF CARCINOGENESIS

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23. TWO INDEPENDENT ASPECTS OF TUMOR PROMOTION.

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24. BURKITT'S LYMPHOMA.

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25. REVIEW ARTICLE. REGULATION OF EXPRESSION OF THE INTEGRATED RETROVIRUS GENOME.

Weinberg RA, Steffen DL
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J Gen Virol; 54(part1):1-8 1981

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26. THE DEVELOPMENT AND VALIDATION OF MUTAGENICITY SCREENING TESTS.

Durkin PR, Santodonato J
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Merill Lane, Syracuse, NY, 13210
Tappi; 64(9):153-159 1981

27. SHORT-TERM TEST SYSTEMS FOR POTENTIAL MUTAGENS AND CARCINOGENS: I. MICROBIAL TESTS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Tests (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903:; OK-81/03:124pp. 1981

28. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.

Eveson JW
Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(3):129-146 1981

29. THE CHROMOSOMES IN HEMATOLOGY.

Berger R
Laboratoire de Cytogenetique, Institut de Recherches sur les Leucemies et les Maladies du Sang, UER d'Hematologie, Hopital Sant-Louis, 2 place du Dr. Fournier, 75475 Paris Cedex 10, France
Cancer Genet Cytogenet; 4(1):69-88 1981

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HORMONAL CARCINOGENESIS

SERIES CK05 No. 82/02 FEBRUARY, 1982

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In this issue:

- **ORAL CONTRACEPTIVES AND HUMAN CANCER** 1-4
- **ORAL CONTRACEPTIVES AND HUMAN HEPATIC ADENOMA** 5
- **ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER** 6
- **MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES** 7-9
- **HORMONAL CARCINOGENESIS IN ANIMALS** 10-11
- **REVIEWS AND OTHER RELATED STUDIES** 12-22

ORAL CONTRACEPTIVES AND HUMAN CANCER

1. AN EPIDEMIOLOGIC STUDY OF EPITHELIAL CARCINOMA OF THE OVARY.

Hildreth NG, Kelsey JL, LiVolsi VA, Fischer DB, Holford TR, Mostow ED, Schwartz PE, White C
(c/o Kelsey) Dept. Epidemiology, Yale Univ. Sch. Medicine, P.O. Box 3333, New Haven, CT, 06510
Am J Epidemiol; 114(3):398-405 1981

A case-control study to identify risk factors for epithelial ovarian cancer was undertaken among women in the age group 45-74 yr who had been admitted to seven hospitals in Connecticut between July, 1977, and March, 1979. Characteris-

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tics that were found to increase the risk of epithelial ovarian cancer included being white, never having been pregnant, having a late age at menopause, having a family history of cancer of the ovary or endometrium, and having a long estimated number of yr of ovulation. Prior use of postmenopausal estrogens did not alter the risk for epithelial ovarian cancer, but there was some indication that oral contraceptives protect against ovarian cancer. Women with ovarian cancer were somewhat more likely to have had a history of an underactive thyroid and were somewhat less likely to have had a history of an overactive thyroid than controls, although these trends were not statistically significant. (Author abstract) (20 Refs)

2. A PROSPECTIVE COHORT STUDY OF ORAL CONTRACEPTIVES AND BREAST CANCER.

Trapido EJ

Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA, 02115

JNCI; 67(5):1011-1015 1981

In 1970 a questionnaire was sent to 97,300 married women aged 25-50 yr residing in eastern Massachusetts. Information was requested on use of oral contraceptives (OC), education, and gynecologic and reproductive histories. Subsequent questionnaires were sent in 1973 and 1979 to a subset of the original cohort (37,000) to obtain recent information. Surveillance of 34 hospitals disclosed 622 cases of breast cancer among respondents diagnosed in a 6-1/2 yr period. The rate ratio of breast cancer associated with any use of OC was 0.84 (95% confidence limits: 0.7, 1.1). Although certain subgroups of users experienced significantly lower rates of hospitalization for breast cancer than did nonusers (including users aged 25-29, those for whom less than or equal to 5 yr had passed since first use, women with ages at birth of first child either before 25 or after 30, and women who first used OC after the birth of the first child), the risk of breast cancer was not consistently lower among users of OC. Among nulliparous women, the rate ratio associated with use of OC was 2.1 (0.9, 5.0). (Author abstract) (20 Refs)

3. ORAL CONTRACEPTIVES AND RISK OF OVARIAN CANCER.

Willett WC, Bain C, Hennekens CH, Rosner B, Speizer FK

Channing Lab., Harvard Medical Sch., 180 Longwood Ave., Boston, MA, 02115

Cancer; 48(7):1684-1687 1981

Among a large cohort of married, female, registered nurses under 55 yr of age, oral contraceptive (OC) use was examined in women with ovarian cancer and 470 age-matched controls. Use of OCs before the diagnosis of cancer was reported by 28% of the women with ovarian cancer and 33% of the controls, yielding a relative risk of 0.8 (95% confidence limits 0.4-1.5). This apparent inverse relationship was attributable to a large effect in women 35 yr of age or younger (relative risk = 0.2, 95% confidence limits 0.1-1.0). Patients with ovarian cancer were 2.2 times more likely than controls to be nulliparous. These data provide reassurance that OC use is not likely to be associated with any major increase in risk of ovarian cancer, but suggest that future studies of this relationship need to consider the possible confounding effect of infertility. (Author abstract) (12 Refs)

4. NEOPLASIA AND HORMONAL CONTRACEPTION.

Huggins GR

Univ. Pennsylvania Sch. Medicine, Philadelphia, PA, 19104

Clin Obstet Gynecol; 24(3):903-925 1981

The relationships between use of oral contraceptives and neoplasia are reviewed. Problems of investigation include lack of suitable animal models, lag time following exposure to carcinogens before development of overt malignancy, low incidence of malignancies in young women, and the wide range of factors influencing neoplasia. Investigative methods include case reports, disease rates and trends, case comparisons, and cohort studies. Breast disease is discussed with respect to the preclinical phase of breast cancer, breast cancer and chronic mastitis, the estradiol hypothesis, and the relationships between oral contraceptive use and benign and malignant breast disease. The relationships of oral contraceptives to liver tumors, pituitary tumors, endometrial hyperplasia, cervical neoplasia, ovarian disease, and choriocarcinoma are evaluated based on current published data. (56 Refs)

ORAL CONTRACEPTIVES AND HUMAN HEPATIC ADENOMA

5. LIVER TUMOURS IN PREGNANCY, FOLLOWING PREVIOUS INTAKE OF HORMONAL CONTRACEPTIVES.

Pietsch P, Petermann J, Zipprich B, Schwesinger G, Kagel KO
Universitats-Frauenklinik, Wollweberstr. 1, DDR-2200 Greifswald, E. Germany
Zentralbl Gynaekol; 103(13):772-780 1981

Liver tumors developed in two women during pregnancy which followed discontinuation of hormonal contraception. Liver cell adenoma developed in a secundipara, 24 yr of age, and its rupture during puerperium led to death by bleeding, after surgical intervention had failed. Hepatocellular carcinoma was recorded from a secundipara, 22 yr of age, and surgically treated, following premature delivery. Problems of diagnosis and the need for interdisciplinary cooperation are discussed and compared with literature data. The pathogenesis of liver tumors in the wake of exogenous hormone inflow and in the context of subsequent pregnancy is another topic of discussion. (Author abstract) (33 Refs) (In GER)

ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER

6. DETECTION OF HUMAN PLACENTAL LACTOGEN IN SERA AND TUMOURS OF PATIENTS WITH FIBROADENOMA OF BREAST.

Sheth NA, Adil MA, Suraiya JN, Sheth AR
Cancer Res. Inst., Parel, Bombay 400 012, India
Br J Cancer; 44(2):258-261 1981

While human placental lactogen (hPL) has been reported associated with malignant tumor, a study is presented which shows its presence in sera of 9/30 women with fibroadenoma of the breast while it was not detected in 30 normal non-pregnant women and 30 normal men. A sensitive radioimmunoassay was used for determination of hPL in tumor extracts and pre- and postoperative sera from patients. In a study of tumors from 21 patients, 9 extracts were positive for hPL. These nine patients (6 with unilateral and 3 with bilateral tumors) also showed hPL in preoperative sera. Twelve other patients (9 with unilateral and 3 bilateral tumors) showed no circulating hPL. Postoperative sera from seven of the nine patients with hPL in their tumors and preoperative sera became negative for hPL 1 wk to 6 mo after excision of fibroadenoma. In the case of bilateral tumors, the presence of hPL in both breasts suggests the possibility of a common factor governing ectopic secretion in both sites. The study indicated a greater production of hPL than beta human chorionic gonadotropin (beta-hCG) in sera of patients with fibroadenoma of the breast. These reports suggest a key role for hPL in the etiology of human benign breast tumors. (13 Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES

7. THE EFFECTS OF IONIZING RADIATION AND OESTROGEN TREATMENT ON THE STEROID-RECEPTOR CONCENTRATIONS IN EXPERIMENTAL MAMMARY CARCINOMA.

Janssens JP, Wittevrongel C, Van Dam J, Goddeeris P, Lauwerijns JM, De Loecker M

Dept. Biochemistry, Faculty Medicine, Univ. Louvain, B-3000 Leuven, Belgium

Biochem Soc Trans; 9(1):95-96 1981

Mammary carcinoma was induced in Sprague-Dawley rats by intragastric injection of 7,12-dimethylbenz[a]anthracene. Tumors appeared after 3 mo. Some rats were irradiated with 20 Gray from a cobalt teletherapy source. Some were treated for three days by sc injection of 5 ug 17beta-estradiol (EDB). Controls remained untreated. Steroid receptor concentrations were determined 40 hr after final hormone treatment or up to 65 days after irradiation. Tumor regression to 25% of pretreatment size occurred during the first 30 days after irradiation. Renewed growth followed, reaching 90% of the pretreatment size by 65 days. EDB-receptor concentrations fell from 2.56 femtomoles/mg (fm/mg) to 1.09 fm/mg during the first 30 days. They remained at the low level during tumor regrowth. Progesterone-receptor levels fell from a control level of 7.39 fm/mg to 1.83 fm/mg during tumor regression and increased during tumor regrowth to 2.36 fm/mg at 65 days. EDB treatment at 65 days restored progesterone-receptor levels to normal control values. EDB-receptor concentrations were not affected by EDB treatment. Evidently the EDB-receptor system, which is necessary for the stimulation of the progesterone-receptor system, remains intact and active after irradiation, although the concentration of receptors is reduced. Interpretation of receptor concentrations measured during endocrine and radiation therapy should be made as a function of these factors. (9 Refs)

8. NEW ASPECTS IN THE DEVELOPMENT OF CYTOTOXIC-LINKED ESTROGENS FOR THE CONTROL OF BREAST NEOPLASIA.

Leclercq G

Laboratoire de Cancerologie mammaire, Service de Medecine, Institut J. Bordet, 1 000 Brussels, Belgium

Arch Geschwulstforsch; 51(7):643-649 1981

The selection and use of cytotoxic-linked estrogens, which bind to estrogen receptors (ERs) and thereby specifically concentrate in the target tissues including breast neoplasms, are described. The selection of these agents is based upon their binding ability to cytoplasmic ERs, their cytotoxicity against two human breast cancer cell lines (ER+ MCF-7 and ER- Evas-T), and their endocrinologic properties and toxicology. Four epoxide derivatives of 17-beta-estradiol and 17-alpha-estradiol were found to reversibly bind with ER but showed no cytotoxicity against MCF-7 and Evsa-7 cell lines. Nitrogen mustard derivatives of hexestrol, diethylstilbestrol, and estrone displayed binding affinity for ER and cytotoxicity against MCF-7 cells. Only the two mononitrogen mustard derivatives of estrone inhibited growth of Evsa-7 cells. This indicated that these nitrogen mustard derivatives had a weaker effect on the Evsa cell line, consistent with the hypothesis of a participation of ERs in their cytotoxic action. The results indicated that the linking of a cytotoxic group on an estrogen in an appropriate position can yield a drug with a significant binding affinity for ERs. The therapeutic implications of these findings are discussed. (13 Refs)

9. LUTROPIN RECEPTORS IN NORMAL AND TUMOUR LEYDIG CELLS.

Cooke BA, Dix CJ, Magee-Brown R

Dept. Biochemistry and Chemistry, Royal Free Hosp. Sch. Medicine, Univ. London, 8 Hunter St., London WC1N 1BP, England

Biochem Soc Trans; 9(1):40-42 1981

Leydig cells from normal adult mouse and rat testes and a Leydig cell tumor can be separated into two cell populations (both containing lutropin receptors) which differ in density and steroidogenic responsiveness. The etiology of these cell types is unknown. They may reflect different phases in a cell cycle. Treatment with gonadotropin (lutropin or human choriogonadotropin) in vivo has been shown to result in the loss of lutropin receptors, a reduction in adenylate cyclase activity, and reduced steroidogenesis; treatment of rats with gonadotropin results in reduced sensitivity of Leydig cells to lutropin in vitro. Tumor cells of density 1.07 g/ml were exposed in vitro to lutropin (0.0, 10, 100, or 1,000 nanog/ml) and exhibited an initial increase in number of lutropin receptors. This reached a max in the controls after 2 hr and remained constant thereafter. All lutropin-treated cells showed decreased binding of choriogonadotropin after 1-2 hr incubation. Basal production of cyclic AMP initially reflected pretreatment with lutropin. Cyclic AMP rose sharply within 1 hr and returned to normal pretreatment levels by 4 hr. Reduction in binding of choriogonadotropin was inhibited by cycloheximide, which prevented lutropin-induced desensitization of adenylate cyclase activity. Results indicate that desensitization of Leydig cell s can be induced in vitro, and loss of both lutropin receptors and adenylate cyclase activity occurs simultaneously; both processes depend on protein synthesis. (16 Refs)

HORMONAL CARCINOGENESIS IN ANIMALS

10. PRODUCTION OF OVARIAN TUMORS BY HORMONE ADMINISTRATION.

Araki S
Dept. Obstetrics and Gynecology, Kurume Univ. Sch. Medicine, Kurume 830, Japan
Kurume Med J; 28(1):35-43 1981

The influence of hormone administration on tumor production was studied in female Wistar rats implanted with chemical carcinogens (9,10-dimethyl-1,2-benzathracene (DMBA), 20-methylcholanthrene, (MC), 3,4-benzpyrene (BP), or 4-nitroquinolin-N-oxide (NQO)). The hormones were an estriol preparation (EST), a progesterone preparation (PROG), a testosterone preparation (AND), a dexamethasone preparation (ACH), and human chorionic gonadotropin (HCG). The incidence of solid tumors was highest with DMBA, less with MC and lowest with BP and NQO. ACH and EST appeared to accelerate tumor growth: the incidence of solid tumors at 20 wk was not significantly different, while at 40 wk it increased to 90% in the ACH group. Up to 20 wk in the hormone-treated groups, tumor incidence was low; however, the tumor incidence increased thereafter. The highest total incidence of cystic tumor was found in the EST group, compared to controls. The solid tumors included fibromas, sarcomas, and adenocarcinomas. In the AND, PROG, and EST groups, the tumors were either fibroadenomas or fibromas. In the HCG group fibroadenomas predominated. Sarcomas appeared in the 30th and 40th wk in the controls and the EST and PROG groups, respectively. The av wt of the tumors produced by ACH and EST was greater than the control, with the largest tumor in the EST group. (27 Refs)

11. MELATONIN INHIBITION AND PINEALECTOMY ENHANCEMENT OF 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMORS IN THE RAT.

Tamarkin L, Cohen M, Roselle D, Reichert C, Lippman M, Chabner B
Intramural Res. Program, Natl. Inst. Child Health and Human Development, NCI, NIH, Bethesda, MD, 20205
Cancer Res; 41(11,part1):4432-4436 1981

The effects of the pineal hormone, melatonin, and of pinealectomy on the incidence of mammary adenocarcinoma in Sprague-Dawley rats treated with 7,12-dimethylbenz(alpha)anthracene (DMBA) were investigated. Melatonin (2.5 mg/kg), begun on the same day as DMBA (15 mg) treatment and given daily in the afternoon for 90 days, significantly reduced the incidence of mammary tumors from 79% (control) to 20% (treated) (p less than 0.002). Rats pinealectomized at 20 days of age and treated with 7 mg of DMBA at 50 days of age had a lighter incidence of tumors (88%) compared to control animals (22%). Fifteen mg of DMBA, which resulted in a higher incidence of tumors, reduced the difference between pinealectomized and control animals. Melatonin only partially reversed the effects of pinealectomy, reducing the incidence from 87% (pinealectomy alone) to 63% (pinealectomy plus melatonin); however, the tumor incidence was still lower (27%) in nonpinealectomized, melatonin-treated animals. Assessment of plasma prolactin, luteinizing hormone, follicle-stimulating hormone, estradiol, and cortisol in DMBA-treated tumor-free and tumor-bearing animals revealed a significantly lower plasma prolactin concentration [27 +-5 (SE)ng/ml] in melatonin-treated animals as compared to vehicle-treated animals [65 +-8 ng/ml]. The concentration of plasma prolactin was less in melatonin-treated, pinealectomized rats (55 +-10 ng/ml) as compared to vehicle-treated, pinealectomized animals (101 +-13 ng/ml). Other hormones were not affected by melatonin treatment. These data support the hypothesis that melatonin inhibits the development of DMBA-induced mammary tumors in the rat while removal of the pineal gland stimulates development of such tumors. Additionally, these experiments provide evidence that these effects may be mediated by a suppression of plasma prolactin levels. (Author abstract) (28 Refs)

REVIEWS AND OTHER RELATED STUDIES

12. BIOCHEMICAL MECHANISM OF MODULATION OF SKIN CARCINOGENESIS BY RETINOIDS.

Verma AK
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Center, Madison, WI, 53706
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

Investigations of mechanisms involving retinoids in the two-stage model of mouse skin carcinogenesis are reviewed. Application of retinoic acid (RA) 1 hr before application of 12-O-tetradecanoylphorbol-13-acetate (TPA) led to inhibition of induction of ornithine decarboxylase (ODC) and resultant putrescine accumulation, and inhibition of enhanced DNA synthesis at 18 hr, but not at 24 or 48 hr. RA did not inhibit S-adenosylmethionine decarboxylase induction, incorporation of [3H]leucine or [3H]histidine into epidermal protein, induction of cyclic AMP phosphodiesterase activity, accumulation of prostaglandins E and F, or hyperplasia occurring 1 or 3 days after TPA treatment. No increase in polyamine biosynthesis was detected after topical skin treatment with 17 nanomole RA, but incorporation of [3H]thymidine increased at 42 hr. RA inhibited skin papillomas and carcinomas when administered with TPA treatments, but not when given with initiating doses of 7,12-dimethylbenz[a]anthracene (DMBA) after repeated TPA doses. RA did not promote growth of DMBA-induced tumors. Combined RA and DMBA treatment did not result in inhibition of induction of ODC or tumors. (58 Refs)

13. CURRENT CONCEPTS IN THE MANAGEMENT OF BREAST CANCER.

Paschold EH, Muss HB
(c/o Muss) Dept. Medicine, Bowman Gray Sch. Medicine, 300 S. Hawthorne Road, Winston-Salem, NC, 27103
Am Fam Physician; 24(3):119-126 1981

Patient evaluation, therapeutic options, and new developments in the treatment of primary and metastatic breast cancer are reviewed. Recent studies have demonstrated that less radical procedures may be as effective as more extensive procedures. The goals of primary treatment is to remove all obvious tumor, to obtain adequate tissue for steroid receptor analysis, and to examine the axillary contents. Axillary dissection should be performed in all patients with primary tumors. Needle biopsy is helpful for patients who are undecided about the choice of primary treatment. Primary treatment of patients with advanced disease must be individualized. Radionuclide scans may be useful in the perioperative evaluation, while tumor marker assays are not cost-effective in patients with early-stage disease or in perioperative management. Steroid receptor assays should be obtained on all primary tumors. Adjuvant therapy has generally been reserved for patients at high risk for recurrence. The use of hormonal therapy alone is controversial. Adjuvant chemotherapy may be useful in selected patients. Current therapy for advanced breast cancer is palliative; cures are rare. Complications arising in breast cancer patients include bone metastases, hypercalcemia, CNS metastases, and spinal cord compression. Breast reconstruction is briefly discussed. (8 Refs)

14. SERUM ANDROGEN LEVELS AND THE MENSTRUAL CYCLE IN WOMEN WITH BENIGN OR MALIGNANT BREAST DISEASE.

England PC, Sellwood RA, Knyba RE, Irvine JD
(c/o Knyba) Dept. Clinical Endocrinology, Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Clin Oncol; 7(3):213-219 1981

Serum levels of dehydroepiandrosterone sulfate have been determined in blood specimens taken over the menstrual cycle in 10 normal women and 28 patients with benign and malignant breast disease. There was no consistent or statistically significant correlation between the amounts of serum dehydroepiandrosterone sulfate and estradiol. This finding does not support the suggestion that the subnormal levels of androgens, in women with high risk of breast cancer and patients with a poor prognosis, reflect alterations in estrogen secretion. (Author abstract) (19 Refs)

15. REVERSIBLE INHIBITION OF RAT HEPATOCYTE PROLIFERATION BY HYDROCORTISONE AND ITS EFFECT ON CELL CYCLE-DEPENDENT HEPATOCARCINOGENESIS BY N-METHYL-N-NITROSOUREA.

Kaufmann WK, Kaufman DG, Rice JM, Wenk ML
(c/o D. Kaufman) Dept. Pathology, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Cancer Res; 41(11,part1):4653-4660 1981

The susceptibility of hepatocytes to carcinogenesis in vivo may be influenced by the phase of the cell cycle at which carcinogen-induced damage is incurred. In order to better understand this relationship, hepatic cell proliferation in juvenile male Fischer 344 rats was charted following a two-thirds partial hepatectomy. For hepatocytes, two distinct waves of DNA synthesis occurred which were followed after 6 to 8 hr by waves of mitotic cell division. In contrast to this kinetic pattern, when hydrocortisone was given after the partial hepatectomy, the initial waves of DNA synthesis and mitosis by hepatocytes were each delayed by about 15 hr. In rats not given hydrocortisone, susceptibility to hepatocarcinogenesis by N-methyl-N-nitrosourea was greatest at 20 hr after partial hepatectomy when the peak fraction of proliferating hepatocytes was in the S phase. By shifting the time of onset of DNA synthesis, the hydrocortisone treatments also shifted the time with greatest sensitivity to N-methyl-N-nitrosourea, with hepatocytes in late G1 or S again the most susceptible. Numerous tumors were also induced by N-methyl-N-nitrosourea in extrahepatic tissues, including intestine, Zymbal's gland, nervous system, kidney, odontogenic tissues, and peritesticular mesothelium. The results illustrate the importance of cell proliferation in carcinogenesis and further point to the specific sensitivity of certain cell cycle phases. (Author abstract) (31 Refs)

16. MEASUREMENT OF DIETHYLSTILBESTROL IN PLASMA FROM PATIENTS WITH CANCER OF THE PROSTATE.

Kemp HA, Read GF, Riad-Fahmy D, Pike AW, Gaskell SJ, Queen K, Harper ME, Griffiths K
(c/o Read) Tenovus Inst. Cancer Res., Welsh Natl. Sch. Medicine, Heath, Cardiff, CF4 4XX, Wales
Cancer Res; 41(11,part1):4693-4697 1981

A specific radioimmunoassay has been developed for diethylstilbestrol (DES), using an antiserum raised against DES monocarboxymethyl ether and a tritium-labeled radio-ligand. Prior to radioimmunoassay, a fraction enriched in DES is obtained from a dichloroethane extract of plasma using Sephadex LH-20. The specificity of the assay is good, and the sensitivity (130 pg/ml) is adequate for accurate determination of DES in plasma from prostatic cancer patients treated with the drug. The precision is satisfactory, with an interassay coefficient of variation of approx 10% at concentrations of approx 1 ng/ml, and the blank values are negligible. Excellent agreement (r = 0.96) is observed between data obtained by radioimmunoassay and those obtained by a procedure using gas chromatography-high-resolution mass spectrometry. DES concentrations in the plasma of six treated (1 mg DES tds) patients were in the range 0.15 to 6.0 ng/ml. Increases in plasma concentration were observed within 2 hr of administration, with secondary rises occurring 5 to 6 hr later. Plasma testosterone concentrations were low in four of the patients; in a single subject, relatively high levels of testosterone were further elevated following administration of luteinizing hormone-releasing hormone. (Author abstract) (19 Refs)

17. TRANSFORMATION OF HAMSTER EMBRYO CELLS BY NEUTRAL STEROLS AND BILE ACIDS.

Kelsey MI, Pienta RJ
NCI, Landow Building, Room 8C25, Bethesda, MD, 20205
Toxicol Lett; 9(2):177-182 1981

Toxicity and transformation data on the neutral sterols cholesterol-alpha-epoxide and cholestan-3beta,5alpha, 6beta-triol (Triol), and on primary (cholic and chenodeoxycholic) and secondary (lithocholic and deoxycholic) bile acids are presented. Previous results showed that 10 ug/ml cholesterol is neither toxic nor cell- transforming. Cholesterol-alpha-epoxide was toxic to 50% (TD50) of cultured Syrian hamster embryo cells at 10 ug/ml, whereas TD50 for Triol occurred at a concentration 1/5 that of its precursor. In the bile acid series, the primary bile acids were less toxic than the secondary derivatives. The latter were less toxic than the oxygenated sterols. Transformation occurred at all doses tested for the oxygenated sterols. Relative cloning efficiencies compared with those found for controls at the highest doses tested were 87% and 70% for cholesterol-alpha-epoxide and Triol, respectively. The primary bile acids were toxic at 480 ug/ml (cholic acid) and 208 ug/ml (chenodeoxycholic acid), and deoxycholic acid had a cloning efficiency of 82% at the highest dose causing cell transformation. Results indicated that mammalian cell transformation may be a preferable short-term assay for structure-activity information of steroid derivatives as well as for potential carcinogenicity. (23 Refs)

18. HORMONAL RELATIONSHIPS, RECEPTORS, TUMOUR MARKERS.

Harper ME, Chaisiri P, Slade J, Peeling WB, Griffiths K

Tenovus Inst. for Cancer Res., Welsh Natl. Sch. Medicine, Cardiff CF4 4XN, Wales

Recent Results Cancer Res; 78:44-59 1981

The endocrine factors concerned with the etiology of cancer of the prostate are unclear. Hormones and glands that could be concerned in controlling the growth and function of the prostate gland include testosterone, adrenal androgens, sex hormone-binding globulin, prolactin, and others. The relationship between hormone concentrations in the plasma of patients with proven prostatic cancer and various clinical parameters was investigated. While promotion of prostatic neoplasia may be dependent on some particular, abnormal endocrine status of certain individuals, it will be difficult to identify a high-risk group from simple plasma analysis of hormones. Radioimmunoassays for salivary steroids might allow a more detailed study of the chrono-endocrinology relating to aging and prostate cancer. The value of androgen receptor assays in human prostatic carcinoma as a predictor of endocrine response has not yet been established. It is possible that an increased responsiveness to normal hormone levels in plasma may be caused by biochemical changes within the prostatic cells. The use of polyamines and acid phosphatase as tumor markers is discussed. Spermine and spermidine levels did not relate to primary tumor staging or the metastatic status of the patient, and their values were of little value in detecting or in monitoring response to therapy. Serum acid phosphatase activity is elevated in patients with prostatic carcinoma, 65-90% of patients with bone metastases, and 5-10% of those with clinically demonstrable metastatic cancer. The prostatic portion of acid phosphatase must be defined. An immunoassay for that purpose is described. (65 Refs)

19. MORPHOLOGICAL DETECTION OF HORMONE TREATMENT IN BARROWS.

Lauwers H, Gyselbrecht C, Simoens P, Nicaise N, De Vos NR

Dept. Veterinary Anatomy, Univ. Ghent, Casinoplein 24, B-9000 Ghent, Belgium

Arch Lebensmittelhyg; 32(3):77-82 1981

Morphological changes induced by hormone treatment in barrows was studied as a means of detection of illegal use of hormones in animals raised for food. A total of 113 male Belgian pigs were castrated before the 10th wk of life and fatted on a conventional diet. Some barrows were given various combinations of diethylstilbestrol (DES), trenbolone, and methyltestosterone. DES injections produced a marked enlargement of the vesicular and bulbourethral glands. Microscopic changes included hyperplasia and metaplasia in the urethral epithelium and excretory ducts of the prostate gland, fibrosis in the vesicular glands, cell desquamation and hyperplasia in the collecting ducts of the bulbourethral glands, and increased activity in the bulbourethral glands. Effects varied with the hormone or combination of hormones, method and time of administration, and dose. Trenbolene reduced, but did not eliminate, the effects of DES. Oral administration of DES produced different histological effects from injection, including increased mucous activity in the bulbourethral glands, initiation of secretory activity in the vesicular glands, and increased density of the secretory units of the prostate. Methyltestosterone counteracted orally-administered DES. Morphologic examination of the male accessory glands was recommended as a simple procedure for detecting the use of synthetic hormones in barrows. (26 Refs)

20. PROBABLE MECHANISM FOR THE LOSS OF BARR BODY IN HUMAN FEMALE TUMOR WITH SPECIAL REFERENCE TO BREAST CANCER.

Ghosh SN, Shah PN

Endocrinology Div., Cancer Res. Inst., Parel, Bombay 400 012, India

Med Hypotheses; 7(8):1099-1104 1981

The relationship between Barr body frequency (BBF) and human female breast tumors is discussed. A decrease in BBF has been observed in colonic neoplasms. This decrease in BBF is possibly related to reactivation of the second X chromosome with concurrent increase in glucose-6-phosphate dehydrogenase activity. Factors that may be involved in the reactivation of a genetically inactive X chromosome are discussed. Studies of post-menopausal women, G-6PD activity in carcinogen-induced rat breast tumors, and estradiol-17beta treatment of HeLa cells indicate an association between BBF frequency and estrogen. Evidence that both X-chromosomes are active in clonal cultures of undifferentiated female mouse teratocarcinoma stem cells derived from spontaneous ovarian tumors has been presented. Other evidence suggesting that activation of a second X-chromosome is not the true mechanism for loss of X-chromatin is presented. Evidence suggesting that low Barr body counts in highly malignant human breast tumor could be related to elaboration of collagenase from tumor cells at the time of invasion is presented. (35 Refs)

21. LONG-TERM ISOGRAFTS OF CULTURED FETAL MOUSE PANCREATIC ISLETS. THE ONCOGENIC EFFECTS OF STREPTOZOTOCIN AND THE PREVENTION OF DIABETIC RENAL COMPLICATIONS.

Mandel TE, Hoffman L, Carter WM

Walter and Eliza Hall Inst. Medical Res., Post Office Royal Melbourne Hosp., Victoria, 3050, Australia

Am J Pathol; 104(3):227-236 1981

Female CBA mice made diabetic with a single iv dose of streptozotocin (STZ) were either grafted with cultured fetal mouse pancreatic islets onto the splenic capsule, treated with insulin, or left untreated. An age- and sex-matched group of nondiabetic mice served as normal controls. All islet-grafted and most insulin-treated mice survived and had normal fasting blood glucose levels. By contrast, of the untreated diabetic mice, one died and the survivors showed poor wt gain. Light-microscopic examination of the islet isografts showed a progressive increase in graft size and beta-cell granulation over the 9-mo study period. Quantitative electron-microscopic examination of the kidney showed that, whereas the islet-grafted and nondiabetic control mice had similar glomerular capillary basement membrane (GCBM) thickness, the untreated diabetic and insulin-treated mice had markedly thickened GCBM. All STZ-treated mice developed diffuse hepatic dysplasia and, at later time points, some showed biliary hyperplasia, intrahepatic cysts, and occasionally nodular dysplasia. With increasing time after STZ, most mice developed renal adenomas. One untreated diabetic mouse also developed a solitary functional pancreatic beta-cell adenoma. STZ effects were not affected by treatment of diabetes. (Author abstract) (46 Refs)

22. SEX DIFFERENCES IN THE EFFECTS OF RETINOIDS ON CARCINOGENESIS BY N-NITROSOBIS(2-OXOPROPYL)AMINE IN SYRIAN HAMSTERS.

Birt DF, Sayed S, Davies MH, Pour P
Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, 42nd and Dewey A ve., Omaha, NE, 68105
Cancer Lett; 14(1):13-21 1981

Male and female Syrian hamsters received a single dose of N-nitrosobis(2-oxopropyl)amine (BOP: 40 mg/kg, sc) and 1 wk later were fed one of four retinoid types (13-cis-retinoic acid (13-cis-RA), N-ethylretinamide (ERA), 2-hydroxy-ethylretinamide (OH-ERA), or 4-hydroxyphenylretinamide (PRA)) each at three dose levels reported as 0.05, 0.1, and 0.2 milliM/kg diet. The wt of the pancreas was influenced by the sex and retinoid level: wt increased in females fed the high retinoid level and decreased in males fed the 0.1 milliM level. Nearly all animals developed pancreatic adenomas. The av number of adenomas was reduced in female hamsters fed retinoids. The greatest decrease occurred with 13-cis-RA (48% reduction), with reductions intermediate for ERA and OH-ERA (39%), and smallest for PRA (14%). In male hamsters, pancreatic adenoma incidence was not influenced by retinoid treatment; however, the multiplicity of these lesions in males fed OH-ERA and PRA was greater than those fed 13-cis-RA, ERA, or control diet. The pancreatic carcinoma incidence was not influenced by retinoids, although female hamsters fed 13-cis-RA developed fewer carcinomas per animal than did animals fed ERA. In female, but not male, hamsters, the liver tumor incidence was reduced from 60% to 21% by feeding OH-ERA, and the gallbladder tumor incidence from 60% to less than 10% in females fed 13-cis-ERA and ERA. These results suggest that sex hormones or other sex differences may influence the factors which determine the ability of retinoids to inhibit carcinogenesis. (33 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Adil MA, 6
Araki S, 10
Bain C, 3
Birt DF, 22
Carter WM, 21
Chabner B, 11
Chaisiri P, 18
Cohen M, 11
Cooke BA, 9
Davies MH, 22
De Loecker M, 7
De Vos NR, 19
Dix CJ, 9
England PC, 14
Fischer DB, 1
Gaskell SJ, 16
Ghosh SN, 20
Goddeeris P, 7
Griffiths K, 16
Griffiths K, 18
Gyselbrecht C, 19
Harper ME, 16
Harper ME, 18
Hennekens CH, 3
Hildreth NG, 1
Hoffman L, 21
Holford TR, 1
Huggins GR, 4
Irvine JD, 14
Janssens JP, 7
Kagel KO, 5
Kaufman DG, 15
Kaufmann WK, 15
Kelsey JL, 1
Kelsey MI, 17
Kemp HA, 16
Knyba RE, 14
Lauwerijns JM, 7
Lauwers H, 19
Leclercq G, 8
LiVolsi VA, 1
Lippman M, 11
Magee-Brown R, 9
Mandel TE, 21
Mostow ED, 1
Muss HB, 13
Nicaise N, 19
Paschold EH, 13
Peeling WB, 18
Petermann J, 5
Pienta RJ, 17
Pietsch P, 5
Pike AW, 16
Pour P, 22
Queen K, 16
Read GF, 16
Reichert C, 11
Riad-Fahmy D, 16
Rice JM, 15
Roselle D, 11
Rosner B, 3
Sayed S, 22
Schwartz PE, 1
Schwesinger G, 5
Sellwood RA, 14
Shah PN, 20
Sheth AR, 6
Sheth NA, 6
Simoens P, 19
Slade J, 18
Speizer FK, 3
Suraiya JN, 6
Tamarkin L, 11
Trapido EJ, 2
Van Dam J, 7
Verma AK, 12
Wenk ML, 15
White C, 1
Willett WC, 3
Wittevrongel C, 7
Zipprich B, 5

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1. CHEMICAL COMPOUNDS AND CANCER RISK.
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Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
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Dept. Environmental Hygeine, Karolinska Inst., Stockholm, Sweden
Environ Health Perspect; 40:93-100 1981

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Norseth T
Inst. Occupational Health, Gydas vei 8, Oslo 3, Norway
Environ Health Perspect; 40:121-130 1981

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Kazantzis G
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Environ Health Perspect; 40:143-161 1981

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Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
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Dept. Environmental Hygiene, Karolinska Inst., S-104 01 Stockholm, Sweden
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Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228
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23. ENZYMES INVOLVED IN THE REPAIR OF DAMAGED DNA.
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Zakour RA, Kunkel TA, Loeb LA
Joseph Gottstein Memorial Cancer Res. Lab., Dept. Pathol., Univ. Washington, Seattle, WA, 98195
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HORMONAL CARCINOGENESIS

SERIES CK05 No. 82/03

MARCH, 1982

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In this issue:

- **ORAL CONTRACEPTIVES AND HUMAN CANCER** 1-2
- **ORAL CONTRACEPTIVES AND HUMAN HEPATIC ADENOMA** 3-4
- **ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER** 5-8
- **MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES** 9-11
- **MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES** 12-13
- **HORMONAL CARCINOGENESIS IN ANIMALS** 14-26
- **REVIEWS AND OTHER RELATED STUDIES** 27-54

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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HE 20. 3173/2:

ORAL CONTRACEPTIVES AND HUMAN CANCER

1. THE INFLUENCE OF HORMONAL ORAL CONTRACEPTION ON THE INCIDENCE OF THE INVASIVE CARCINOMA, CARCINOMA-IN-SITU AND DYSPLASIA OF THE CERVIX (MEETING ABSTRACT).

Andolsek L, Kovacic J, Kozuh M, Litt B

Clinical Centre, Department of Gynaecology and Obstetrics, University of Ljubljana, Ljubljana, Yugoslavia

Obstetric and Gynaecology: 8th Asian Congress, October 25-31, 1981, Melbourne, Australia Asia and Oceania Federation of Obstetricians and Gynaecologists 352 pp., 1981.

The aim of this study was to find out the possible influence of hormonal oral contraceptive use on the incidence of cervical invasive carcinoma, carcinoma-in-situ and severe dysplasia . A prospective study of two groups of oral contraceptive users (prior-user and non prior-user group) and one control group of nonusers was carried out. From the recruitment period 1970-1972 till the end of the study in 1976, 5562 non-prior users with 20189 women-yr, 5906 prior-users with 28498 women-yr and 15665 nonusers with 65637 women-yr were followed. During the study 115694 smears were taken. In the non prior-user group group 3 cases of cervical carcinoma (two microcarcinomas and one adenocarcinoma), 19 cases of carcinoma-in-situ and 16 cases of severe dysplasia were found. Corresponding findings in the prior-user group were 3 cases of cervical carcinoma, 19 cases of carcinoma-in-situ and 23 cases of severe dysplasia, and in control group no case of cervical carcinoma, 48 cases of carcinoma-in-situ and 46 cases of severe dysplasia. A significant increase in the incidence of invasive carcinoma (microcarcinoma) among the users was found. For the incidence of carcinoma-in-situ an increase was found only in group of non prior-users in the age group 30-34 yr and using oral contraceptives for 13-24 mo. For the incidence of severe dysplasia no significant difference was found. (no Refs)

2. CANCER RISKS OF MEDICAL TREATMENT. PART II: POTENTIALLY CARCINOGENIC MEDICATIONS IN CURRENT USE.

Schottenfeld D

Dept. Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY

Clin Bull; 11(2):75-82 1981

Experimental and epidemiological data on the carcinogenicity of currently available drugs are reviewed. Patients treated with cytotoxic antineoplastic agents are at increased risk for bladder cancer and acute nonlymphocytic leukemia. Immunosuppressive agents are associated with development of lymphoreticular malignancies in renal transplant recipients. Estrogen administration increases the risk of endometrial and breast carcinoma in menopausal and postmenopausal women. Oral contraceptives have been shown to be associated with endometrial cancer, uterine cervical dysplasia, and cervical carcinoma in situ. Oral contraceptives reduce the risk of benign breast diseases. Androgenic anabolic steroids have been found to cause liver carcinoma. Methoxypsoralen in the presence of UV increases the risk of skin carcinoma. Phenacetin-containing analgesics have been shown to cause chronic interstitial nephritis, carcinoma of the renal pelvis, and bladder carcinoma. Potentially carcinogenic but cost-effective drugs should be prescribed at the lowest dose and for the shortest period of time. (59 Refs)

ORAL CONTRACEPTIVES AND HUMAN HEPATIC ADENOMA

3. THE LIVER AND 'THE PILL'. PART 2: HEPATIC TUMORS.

Eisenburg J

Med. Univ.-Klinik II, Klinikum Grosshadern, Marchioninistrasse 15, 8000 Munchen 70, W. Germany

Fortschr Med; 99(38):1527-1532 1981

The relationship between the use of oral contraceptives and the development of benign or malignant tumors of the liver is discussed. Types of benign hepatic tumors are listed, and features of hepatocellular adenoma and focal nodular hyperplasia and described in detail. Hepatocellular carcinoma is examined with regard to the mechanism of its development, diagnosis, clinical features, prognosis, and treatment. Selected features of the relationship between use of oral contraceptives and occurrence of liver tumors are illustrated through a summary of the case histories of eight patients (22-45 yr old). All of the patients used oral contraceptives for 5 to 14 yr, and all subsequently developed benign liver tumors. Three of the patients were asymptomatic at the time of diagnosis. The final diagnosis was made through laparoscopy in four patients and through laparotomy in four. In one patient, a hepatoma developed in an area of benign focal nodular hyperplasia within 2 yr of the original diagnosis. It is suggested that women who used oral contraceptives for long periods should be screened for hepatic changes at regular intervals. (6 Refs) (In GER)

4. HUMAN LIVER TUMORS IN RELATION TO STEROIDAL USAGE (MEETING ABSTRACT).

Barrows GH, Christopherson WM

University of Louisville School of Medicine, Louisville, KY

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Since 1973, a number of investigators have reported an association between liver neoplasia and steroid usage. Through referral material the authors have examined the histology of over 250 cases of hepatic neoplasia, most in patients receiving steroid medications. The majority have been benign, predominantly focal nodular hyperplasia (55%) and the hepatocellular adenoma (39%). The av age was 31.4 yr. Eighty-three precent had significant steroid exposure with an av duration of 71 mo for focal nodular hyperplasia and 79.6 mo for hepatocellular adenoma. The type of estrogenic agent was predominantly mestranol. A distinct clinical entity of life threatening hemorrhage from the lesion occurred in 31% of patients with hepatocellular adenoma and 9% of patients with focal nodular hyperplasia. Recurrence of benign tumors has occurred in some patients who continued using steroids and regression has been observed in patients who had incomplete tumor removal but discontinued steroid medication. Medial and intimal vascular changes have been present in a large number of the benign tumors. The relationship of these vascular changes to oncogenesis is unclear, but similar lesions have been described in the peripheral vasculature associated with steroid administration. A number of hepatocellular carcinomas have also been seen. Of significance is the young age of these patients and lack of abnormal histology in adjacent non-neoplastic liver. A striking number of the malignant hepatocellular tumors have been of the uncommon type described as 'eosinophillic hepatocellular carcinoma with lamellar fibrosis'. The epidemiology of liver lesions within this series is difficult to assess since the material has been referred from very diverse locations. (no Refs)

ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER

5. BREAST CANCER.

Arseneau JC
Rochester Univ. Sch. Medicine and Dentistry, Rochester, NY
Practical Cancer Chemotherapy. Rosenthal SN, and Bennett JM, ed. Garden City, NY, Medical Examination Publishing Co., 461 pp., 1981.

The etiology, clinical features, and treatment of malignant breast cancers are reviewed. The low incidence of breast cancer in women castrated in youth and in women who have early or multiple pregnancies implicates hormones as factors in etiology, although their role remains unclear. High-risk populations can be defined by exposure to environmental factors, such as ionizing radiation, or genetic factors such as a history of breast cancer in close female relatives. No conclusive evidence has yet linked viruses to human breast cancer. Most breast cancers are ductal type adenocarcinoma. Most lesions present as a painless mass, and signs of metastatic disease may be present either locally (enlarged lymph nodes in axilla, supraclavicular, or cervical areas) or at distant sites such as bone, liver, lung, or brain. Diagnosis of breast cancer is made by biopsy and microscopic examination of the biopsy specimen. A bone scan is often done to search for subclinical metastases. Surgical intervention is the method of choice in the initial management of malignant breast disease, with much current debate concerning particular procedures. In fact, variations in local therapy have little effect on survival. Hormonal and cytotoxic drug therapy is discussed. (44 Refs)

6. FACTORS THAT PROMOTE THE DEVELOPMENT OF HUMAN BREAST CANCER (MEETING ABSTRACT).

Thomas DB
Fred Hutchinson Cancer Research Center, Seattle, WA
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

The epidemiologic features of breast cancer and current hypotheses regarding the etiologic role of endogeneous hormones are summarized and evaluated. The inconsistent results of studies of exogenous hormones and breast cancer are also critically summarized. A proposed model for human mammary carcinogenesis is presented. Hormonal aberrations that vary with reproductive and menstrual events are hypothesized to alter susceptibility of mammary tissue to primary carcinogens. The nature of these aberrations, and the identity of the primary carcinogens are largely unknown. Avenues for further research are suggested. (no Refs)

7. THE RELATIONSHIP BETWEEN DIETARY FAT AND HORMONES IN MAMMARY CARCINOGENESIS (MEETING ABSTRACT).

Dao TL
Roswell Park Memorial Institute, Buffalo, NY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Both epidemiologic findings and experimental data provide convincing evidence to support the concept that the etiology of cancer is multifactorial. In experimental mammary carcinogenesis, polypeptide and steroid hormones have been shown to be involved in the initiation and promotion phases of mammary tumor induction. Among the environmental factors suspected to play a role in mammary carcinogenesis, dietary fat correlates well with breast cancer incidence. This paper will present experimental data to demonstrate the co-carcinogenic effect of hormones in the induction of mammary cancer in the rat by polycyclic aromatic hydrocarbons. The experimental data will be compared with human epidemiologic findings. The relationship between dietary fat and mammary carcinogenesis in experimental models will be presented and, finally, the possible relationship between dietary fat and hormones will be discussed. (no Refs)

8. OTHER IATROGENIC CANCERS (MEETING ABSTRACT).

Ross RK

No affiliation given

The Causes of Cancer, November 6, 1981, Los Angeles, California California Hospital Medical Center; 1981

The majority of iatrogenic cancers fit into two categories: those induced by diagnostic or therapeutic radiation and those induced by prescription drugs. Since radiation induced cancer has already been discussed in detail, this session will be primarily concerned with drugs as causes of human cancer. Several drugs which are now recognized as causes of human cancer have been detected only because of the rarity of the cancer in the absence of the drug. For example, the association between a mother's use of diethylstilbestrol during pregnancy and the development of clear cell adenocarcinomas of the vagina in her daughter decades later was only detected because several cases of this extremely rare tumor were noted in a single hospital in a rather short period of time. Similarly, in a case-control study at University of Southern California, it was demonstrated that risk to women or a rare form of liver cancer, benign liver adenoma, was strongly related to duration of use of oral contraceptives. It seems likely that such relationships exist for more common cancers but go undetected either because no one suspects this relationship or the relationship is difficult to study in the face of other factors causing the same disease. In fact, several such relationships with more common cancer sites have been demonstrated in recent yr. Use of amphetamines has been shown to increase one's risk to Hodgkin's disease some 4-6 fold, use of immunosuppressive drugs has been demonstrated to greatly increase risk to non-Hodkins' lymphomas and use of estrogen replacement therapy, perhaps the most widely studied group of drugs in terms of cancer risk, increases risk of endometrial cancer and breast cancer. (no Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES

9. SIMULTANEOUS DETERMINATION OF ESTROGEN AND PROGESTERONE RECEPTORS USING 125I-ESTRADIOL AND 3H-R5020 (MEETING ABSTRACT).

Thibodeau SN, Freeman L, Jiang NS
Mayo Clinical, Rochester, MN, 55905
Clin Chem; 27(6):1078 1981

We describe a dual-isotope assay for measuring simultaneously the concentration of estrogen and progesterone receptors in tumor cytosols. The concentrations of these receptors are derived from separate Scatchard-plot analyses of a single dextran-coated charcoal (DCC) assay that incorporates both radioiodinated estradiol and tritiated R5020 as the labeled ligands. Competition studies between these radiolabeled ligands and a number of unlabeled steroids (testosterone, estradiol, diethylstilbestrol, cortisol, progesterone, and R5020) revealed that 3HR5020 and 125I-estradiol bound specifically to their respective receptor. In addition, a comparison of several DCC assays, each of which utilized various labeled steroids,(3H-estradiol, 125I-estradiol, 3H-R-5020, or both 125I-estradiol and 3H-R5020) showed that (a) 125I-labeled and 3H-labeled estradiol were equally effective in measuring the concentration of the estrogen receptor (linear regression analysis; y equals 0.98x + 8.99; r equals 0.98; n equals 42) and (b) the concentration of the estrogen and of the progesterone receptors derived from the dual-isotope assay was identical to that obtained from the two respective single-label assays. The dual-isotope DCC assay requires both less time and less tissue because (a) both radiolabeled ligands can be included in the same assay mixture and (b) both radioiodine and tritium can be quantitated simultaneously with a liquid scintillation counter. (no Refs)

10. DUAL COMPONENT ESTRADIOL BINDING IN LEIOMYOMA AND TUMOR BEARING MYOMETRIUM (MEETING ABSTRACT).

Stevens SR, Otubu A, Besch NF, Besch PK
Department of Obstetrics/Gynecology, Baylor College of Medicine, Houston, TX, 77030
Clin Chem; 27(6):1078 1981

Leiomyomas or uterine fibroids are a common estrogen dependent tumor of women. Our purpose was to assay estrogen binding in human leiomyomas and tumor bearing myometrium by Scatchard analysis using a wide concentration range of [3H]-estradiol-17beta in order to demonstrate the presence of two high affinity estrogen binding proteins, and to quantitate and compare the number of binding sites of each component in the two tissues. Leiomyoma and myometrial tissue cytosols were prepared from hystere ctomy specimens from premenopausal women. Serum binding proteins were excluded by receptor precipitation at a final concentration of 30% ammonium sulfate. Unbound steroid was removed by dextran coated charcoal treatment. Two high affinity estradiol binding components presumed to be estrogen receptors were clearly present in both leiomyoma and myometrial cytosols. The concentration of binding sites and the equilibrium dissociation constants (Kd's) of each component were determined by the method of Rosenthal. Nearly identical Kd's of 10(-10) and 10(-9) M were determined for the two components in both tissues. In almost every case the concentration of each estrogen binding component in myomatous tissue was greater than the corresponding concentration in myometrial tissue from the same organ. The difference in concentration of lower affinity sites was larger than the difference in concentration of higher affinity sites and suggests that the role of the lower affinity binding protein may be more significant to the etiology of leiomyomas. (no Refs)

11. PEROXIDASE ACTIVITY IN MAMMARY TUMORS - EFFECT OF TAMOXIFEN.

Levy J, Liel Y, Feldman B, Aflallo L, Glick SM
Div. Endocrinology, Soroka Medical Center, Ben-Gurion Univ. Negev, Beer-Sheva, Israel
Eur J Cancer Clin Oncol; 17(9):1023-1026 1981

Dimethylbenz(a)anthracene (DMBA)-induced tumors in rats were studied for changes in size, cytosolic estrogen (ER) and progesterone (PgR) receptors, and for peroxidase activity before treatment, after 15 days of treatment with the anti-estrogen tamoxifen, and 15 days following cessation of the treatment. Mean size of the tumors decreased significantly during the treatment period to 1/3 the original size and ER and PgR decreased significantly to 1/5 their original levels. Peroxidase activity increased 30-fold. All the changes reversed significantly 15 days after cessation of tamoxifen treatment. These results are consistent with a previous study in which regression of the tumors was induced by castration and recovery was brought about by treatment with estradiol. In DMBA-induced mammary tumors in rats, peroxidase activity in regressing and growing tumors is in inverse relation to changes in tumor size, ER and PgR, which are accepted indicators of estrogenic activity. (Author abstract) (16 Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES

12. STEROID HORMONES AND BREAST CANCER.

Adams JB
University of New South Wales, New South Wales, Australia
Diss Abstr Int [B]; 42(4):1425-B 1981

The thesis contains 49 papers. Early studies were undertaken on the biosynthesis of sulphated mucopolysaccharides (sulphated glycosaminoglycans) in embryonic chick cartilage. Studies were also undertaken on the chemical composition of the ground substance of the stroma of human mamma ry carcinoma tissue and on the mucin of colloid carcinoma of the breast. It was during these latter investigations that the linkage of carbohydrate prosthetic groups, via N-acetylhexosamine to serine and threonine residues, in this and other glycoproteins (including blood group substances) was established. Steroid sulphotransferases were discovered in human adrenal glands and also in human mammary carcinoma tissue and work proceeded on two fronts: firstly, the isolation and properties of steroid sulphotransferases, and secondly, on the biological significance of these enzymes in mammary tumors and other tissues. Intensive investigations were then made on steroid metabolism in human mammary carcinoma tissue and its intrinsic paraendocrine properties were revealed. The above data has been synthesized into a working hypothesis on hormones and breast cancer and the proposal made that C19 steroids unsaturated at position 5 (5-androstene derivatives) of the adrenal gland may be involved in an etiology of the disease. This hypothesis is currently being tested. (no Refs)

13. METABOLIC ACTIVATION OF DIETHYLSTILBESTROL BY PROSTGLANDIN SYNTHETASE AS A MECHANISM FOR ITS CARCINOGENICITY (MEETING ABSTRACT).

Bennett S, Marshall W, O'Brien PJ

Department of Biochemistry, Memorial University of Newfoundland, Newfoundland, Canada

International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The synthetic estrogen diethylstilbestrol (DES) induces kidney tumors in hamsters and genital tract tumors in rodents. Cervicovaginal alterations including carcinoma were also observed in the female offspring of DES treated women, as were certain teratogenic changes in the genital tract of their male progeny as a result of its transplacental toxicity. Metzler et al 1978 have suggested that peroxidases of estrogen target organs are responsible by catalyzing DES oxidation to intermediate that bind to nucleic acids and other cellular macromolecules. Our research shows that prostaglandin synthetase could also be a catalyst. Seminal vesicular microsomes and uterine microsomes readily catalyzed the binding of C14 diethylstilbestrol to DNA and protein in the presence of arachidonate but not NADPH. Similar results were obtained with C14 estradiol and could explain the association of estrogens and cancer of tissues whose growth is effected by estrogen. DES also induces liver necrosis in vivo. Blackburn et al 1977 have shown that liver microsomes with NADPH catalyzes the binding of DES to DNA. We have also found that cumene hydroperoxide is much more effective than NADPH in catalyzing this binding. (no Refs)

HORMONAL CARCINOGENESIS IN ANIMALS

14. EFFECT OF 3,5,3'-TRIIODO-L-THYRONINE ON THE INCIDENCE AND GROWTH KINETICS OF SPONTANEOUS MAMMARY TUMORS IN C3H/HEN MICE.

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Dept. Medicine, Uniformed Services Univ. Health Sciences, Bethesda, MD, 20014

Cancer Res; 41(12):5015-5019 1981

The present study compares the incidence and growth kinetics of spontaneous mammary tumors in 3,5,3'-triiodo-L-thyronine (T3)-treated (0.7 ug/day, ip) C3H/HeN retired breeder mice with tumors occurring spontaneously in this strain (0.15 M NaCl, ip). T3 treatment markedly increased the rate of tumor incidence but had no effect on tumor growth rate as measured by tumor doubling time. A comparison of tumor labeling index and mitotic index between the two groups showed no difference. A histological comparison of the mammary glands in the two groups showed no significant difference in number of hyperplastic alveolar nodules. However, ductal-alveolar development was more pronounced in the 0.15 M NaCl-treated control group; consistent with this observation was the finding of lower levels of serum prolactin in the T3-treated group. Since mammary tumorigenesis was increased in T3-treated mice in spite of lower levels of serum prolactin, a well-known promoter of spontaneous mammary tumor in mice, a direct role for T3 in the process of tumor formation is suggested. (Author abstract) (45 Refs)

15. ONCOGENIC TRANSFORMATION AND THE REDUCTIONS OF INSULIN SECRETION AND PROLIFERATIVE CALCIUM DEPENDENCE DURING REPEATED PASSAGE OF PANCREATIC ISLET CELLS IN VITRO.

Whitfield JF, Boynton AL, Healy GM, Sun AM

Animal and Cell Physiology Group, Natl. Res. Council Canada, Ottawa, Ontario K1A OR6, Canada

Cancer Lett; 14(2):159-168 1981

Changes in calcium-dependent ability to secrete insulin and proliferative calcium-dependence of fetal bovine pancreatic islet cells during passage through successive generations were analyzed. Although the insulin content of fetal pancreas did not change appreciably between passage 3 and 12, insulin secretion fell to non-detectable levels over this period. Proliferation of islet cells could be stopped or greatly lowered by reducing the calcium concentration from 1.8 to 0.02 milliM. However, as with insulin secretion, this sensitivity to extracellular calcium deprivation declined and eventually vanished as the cells passed through successive generations and their proliferative capacity increased. Reductions of insulin secretion and proliferative calcium dependence were accompanied by oncogenic transformation. (29 Refs)

16. AUTORADIOGRAPHIC DEMONSTRATION OF UPTAKE AND RETENTION OF 3H-ESTRADIOL AFTER IN VITRO INCUBATION.

Buell RH, Tremblay G

Dept. Pathology, McGill Univ., Montreal, Quebec H3A 2B4, Canada

J Histochem Cytochem; 29(11):1316-1321 1981

An in vitro incubation method is described for the demonstration of 3H-estradiol in sections of mouse uterus by thaw-mount autoradiography. The method involves the incubation of tissue sections in 5 nM 3H-estradiol with a subsequent 2 hr chase in medium containing 3.5 g% bovine serum albumin. The distribution of the silver grains observed compares favorably to that seen by others with dry-mount autoradiography after in vivo injection. The labeling is inhibited by excess estradiol or diethylstilbestrol, but not by progesterone or hydrocortisone. Its subcellular distribution appears predominantly nuclear in presumptive target cells. Some regional variability in degree of labeling is present throughout the sections, but is far less marked within a given area. Because the observed labeling has been retained during a 2 hr chase and can be inhibited, it is likely to represent physiologically significant uptake and retention of 3H-estradiol in target cells. Preliminary results with human mammary carcinoma suggest this method may be applicable to the investigation of estrogen target cells in human tissue. (Author abstract) (37 Refs)

17. DIFFERENTIATION IN CULTURE OF A RAT MAMMARY STEM CELL LINE (MEETING ABSTRACT).

Rudland PS, Warburton MJ

Ludwig Institute, Royal Marsden Hospital, London, England

International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Three main types of mammary epithelial cells are distinguishable in normal mature glands and in carcinogen induced tumors, those lining the alveoli, those lining the ducts and the myoepithelial cells round both ducts and alveoli. We have previously isolated a clonal epithelial stem cell line from a dimethylbenz(a)anthracene-induced rat mammary carcinoma which can give rise to both alveolar-like and myoepithelial-like cells in culture. The former process can be accelerated by a combination of dimethyl sulphoxide (DMSO) and the mammotropic hormones, prolactin, hydrocortisone and insulin. We now report that the artificial inducer DMSO can be replaced by prostaglandin (PG)E1 and to a lesser extent by PGE2 and PGF2alpha in accelerating this differentiation step. The alveolar-like cells also produce fewer tumors than their parent cells when injected into immunodeprived (nu-nu) mice. Thus this process of differentiation which can be regulated in part by PGE1 in vitro is also accompanied by a reduction in neoplastic potential when the cells are tested in vivo. (no Refs)

18. REDUCED TUMORIGENICITY OF CULTURED NEUROBLASTOMA TREATED WITH DEXAMETHASONE (MEETING ABSTRACT).

Sandquist D, Black AC
Department of Anatomy, University of Iowa, Iowa City, IA
Anat Rec; 199(3):223A 1981

Since dexamethasone has been shown to promote morphological differentiation in C1300 murine neuroblastoma, the effect of dexamethasone on tumorigenicity of cultured neuroblastoma and on de novo synthesis of DNA, RNA and protein was determined. Within 12 hr, dexamethasone caused a dose-dependent inhibition of 3H-thymidine incorporation into DNA. Incorporation of 3H-leucine into protein was not affected by dexamethasone. Incorporation of 3H-uridine into RNA was initially decreased, yet later exceeded control values. Neurite formation was interrupted by inhibition of RNA or protein synthesis. Cells treated with dexamethasone before inoculation into A/J mice produced fewer tumors with longer latent periods compared to controls. About 2.6 x as many neuroblastoma cells treated with 50 ug/ml dexamethasone for 4 days were required for tumor development in 50% of recipient animals as compared to solvent-treated controls. Reduced tumorigenicity was dependent upon the length of treatment and the concentration of dexamethasone used. Cortexolone did not mimic the effects of dexamethasone. If, instead of inoculation, cells were replated and grown without dexamethasone, cellular aggregations appeared among the cells cultured in the absence of dexamethasone. By autoradiography, replated cells previously treated with ethanol displayed uniform incorporation of 3H-thymidine, whereas replated cells from dexamethasone-treated cultures exhibited no incorporation in differentiated cells. However, incorporation was noted among the clusters. (no Refs)

19. THE BINDING OF 7,12-DIMETHYLBENZ[A]ANTHRACENE TO MAMMARY GLAND MACROMOLECULES IN THE HAMSTER: EFFECTS OF ENOVID FEEDING OR TRANSPLACENTAL EXPOSURE TO DIETHYLSTILBOESTROL.

Hertzog PJ, Lawson TA, Gingell R
Cancer Res. Unit, Univ. York, Heslington, York YO1 5DD, England
Chem Biol Interact; 37(1):199-205 1981

The covalent binding of 7,12-[3H]dimethylbenz[a]anthracene ([3H]DMBA) to mammary gland macromolecules was studied in hamsters fed a contraceptive mixture, Enovid, those exposed transplacentally to diethylstilbestrol (DES), and controls. Compared with rats, hamsters are relatively resistant to DMBA mammary carcinogenesis, but susceptibility is increased by either of the above treatments with Enovid or DES. The amount of DMBA bound to DNA and protein was 4-5x greater than to RNA, but only DNA binding was persistent. Fifty-three percent of the DNA-bound DMBA was still present after 8 days. The amount of DMBA bound to hamster mammary DNA and its persistence was similar to that found in rats. Neither Enovid nor DES treatment altered the levels of binding to mammary macromolecules, nor their persistence. These results indicate that the species differences in the susceptibility to DMBA-induced mammary carcinogenesis in hamsters and rats, and modification of the former by hormones, is not due to differences in the activation of carcinogens. The role of hormones such as prolactin in the promotion phase of mammary gland carcinogenesis may explain these differences. (Author abstract) (18 Refs)

20. LIVER REGENERATION AFTER PARTIAL HEPATECTOMY IN ORAL CONTRACEPTIVE-TREATED FEMAL E RATS.

Mukundan MA, Krishnamurthi D, Bamji MS

Natl. Inst. Nutrition, Indian Council Medical Res., Jamai-Osmania (P.O.) Hyderabad-500 007, Andhra Pradesh, India

Biochem Med; 26(2):222-230 1981

Treatment of adult female rats with 1/10th tablet of combination-type oral contraceptive (OC), Ovulen-50 (ethynodiol diacetate, 1.0 mg; ethynyl estradiol, 50 ug) for 24 days resulted in a significant increase in lipid content and a small increase in DNA content (per unit body wt) of the liver. Liver regeneration following partial hepatectomy as judged by increase in liver wt and protein, DNA, and RNA contents was significantly lower in the OC-treated animals compared to the controls. Prior to hepatectomy, thymidine incorporation into DNA was significantly higher in the livers of OC-treated rats. This trend reversed after hepatectomy. Histological examination revealed a higher incidence of binucleate cells and mitotic figures in the livers of OC-treated rats prior to hepatectomy but not during regeneration. (Author abstract) (24 Refs)

21. HYPERENINEMIC HYPOALDOSTERONISM IN ASSOCIATION WITH NEOPLASIA INDUCED HYPERCALCEMIA IN THE FISCHER RAT.

Sowers JR, Sollars E, Nyby MD, Jasberg K, Tuck ML

Endocrine Metabolism Div. (111E), Veterans Admin. Medical Center, 16111 Plummer St., Sepulveda, CA, 91343

Metabolism; 30(10):987-991 1981

Alterations in the renin-angiotensin-adolosterone system in hypertensive, hypercalcemic Fischer rats bearing transplanted Leydig cell tumors were evaluated by measuring plasma aldosterone (PA), plasma renin activity (PRA), and systolic blood pressure (BP) responses to immobilization stress. PA and plasma corticosterone responses to graded ATCH infusions and PA and BP responses to graded angiotensin II (AII) were also evaluated. The results demonstrated marked increases in basal PRA that correlated with the degree of hypercalcemia reached after tumor transplanation. Postive correlations between serum calcium and PRA suggested that increased calcium ion stimulated renin secretion. PRA responses to immobilization stress were increased in tumor-bearing rats. However, basal PA and corticosterone levels were decreased in hypercalcemic rats, as were PA and corticosterone responses to ACTH and PA responsess to immobilization stress and AII. BP responses to immobilization stress and AII correlated positively with serum calcium concentrations. The possibility that the hypertension in these rats was related to a vasoconstrictor effect of calcium on peripheral blood vessels is discussed. (28 Refs)

22. GROSS AND HISTOPATHOLOGIC EFFECTS OF MEDROXYPROGESTERONE ACETATE AND PROGESTERONE ON THE MAMMARY GLANDS OF ADULT BEAGLE BITCHES.

Concannon PW, Spraker TR, Casey HW, Hansel W
Dept. Physiology, Cornell Univ., 820 Veterinary Res. Tower, Ithaca, NY, 14853
Fertil Steril; 36(3):373-387 1981

Medroxyprogesterone acetate (MPA: 0.2-75 mg/kg, im, every 3 mo for 1-1.5 yr) was administered to intact, ovariectomized, or hypophysectomized beagles in groups of 6-12 animals each. Intact, noncycling controls received progesterone implants (3-22 cm/kg). MPA equal or greater than 2.0 mg/kg completely suppressed ovulatory cycles, and the suppression was associated with the maintenance of elevated MPA serum levels. MPA treatment (10 and 75 mg/kg) resulted in an increased incidence of multiple, large mammary gland nodules (5-11 mm). These nodular lesions consisted of simple or complex lobular hyperplasia, simple or complex adenomas, and benign mixed tumors; no malignant tumors were found. The nodules occurred after 4-6 of treatment in older dogs and after 8-15 mo in young dogs. Ovariectomy did not affect tumor induction by 75 mg/kg MPA, but adenoma incidence was significantly lower in hypophysectomized than in intact dogs. Low progesterone doses prevented ovarian cycles and higher doses resulted in some degree of mammary enlargement, glandular activity, and nodular development. (29 Refs)

23. ENHANCEMENT BY RETINYL ACETATE OF HORMONE-INDUCED MAMMARY TUMORIGENESIS IN FEMALE GR/A MICE.

Welsch CW, Goodrich-Smith M, Brown CK, Crowe N
Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824
JNCI; 67(4):935-938 1981

Feeding of retinyl acetate (82 mg/kg ration) for 13-16 wk to estrone- and progesterone-treated nulliparous and multiparous inbred GR/A mice resulted in a substantial increase in the incidence of mammary carcinomas. Mammary carcinoma incidence in nulliparous control and retinoid-fed mice in experiment 1 was 22/65 (34%) and 37/65 (57%) (p less than 0.05), respectively; in experiment 2, 27/48 (56%) and 37/48 (77%) (p less than 0.05), respectively. Mammary carcinoma incidence in multiparous control and retinoid-fed mice in experiment 1 was 13/30 (43%) and 23/30 (77%) (p less than 0.05), respectively; in experiment 2, 19/19 (100%) and 19/19 (100%), respectively. The purported chemopreventive activities of retinyl acetate in murine mammary tumorigenesis were not demonstrated in this study; indeed, the vitamin A analog appeared to enhance this oncogenic process in the steroid hormone-treated GR mouse mammary cancer model. (Author abstract) (25 Refs)

24. THE ROLE OF ESTROGEN IN HEPATIC NEOPLASIA: AN EXPERIMENTAL MODEL (MEETING ABSTRACT).

Wanless IR, Medline A
Toronto Western Hospital, Toronto, Ontario, Canada
Gastroenterology; 80(5,part2):1354 1981

The administration of estrogens to humans has been associated with the development of benign and malignant hepatocellular neoplasms. We present here a rat model which demonstrates that stilbestrol (DES) promotes the development of hepatic noeplasms in rats previously initiated with diethylnitrosamine (DEN). Thirty-two male rats (Fisher 344) were given a single dose of DEN (200 mg/kg, ip) followed 4 wk later by DES (5 mg, po) twice weekly for up to 50 wk. Other rats given vehicle only served as controls. DES was stopped at the time of sacrifice or 11-29 wk prior to sacrifice. All rats given both DEN and DES developed grossly visible hepatic hyperplastic nodules, measuring up to 29 mm in diameter, after 20 wk of DES. Rats given DEN alone or DES alone did not develop nodules. Microscopic hyperplastic foci also developed in rats given DEN plus DES or DES or DEN alone. The foci developing in rats given DES were largely reversible on cessation of estrogen therapy. Mitotic activity in foci and nodules was prominent during estrogen therapy but declined markedly after cessation of therapy. Similar promoting activity of ethinylestradiol (0.2 mg twice weekly) in male rats and of DES in female rats was observed. The data indicate that estrogens promote neoplasia, perhaps by increasing hepatocytic mitotic activity thereby allowing previously initiated cells to evolve into neoplastic clones. Although comparison with human disease should be made with caution, the parallels to human oral contraceptive-associated hepatic adenomas and carcinomas is obvious. It is possible that some women have latent 'initiated' cells that are unusually responsive to estrogen. (no Refs)

25. ORAL CONTRACEPTIVE STEROIDS AS PROMOTERS AND COMPLETE CARCINOGENS FOR LIVER IN FEMALE SPRAGUE DAWLEY RATS (MEETING ABSTRACT).

Yager JD
New York University Medical School, New York, NY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Recent reports have described an increased incidence of adenomas and hepatocellular carcinomas in livers of women with a history of long-term oral contraceptive use. Evidence derived from human and experimental animal data suggests that oral contraceptive steroids may be liver tumor promoters. Studies being carried out in my laboratory were designed to determine whether two oral contraceptive steroids, mestranol and norethynodrel, can promote diethylnitrosamine (DEN)-initiated hepatocarcinogenesis. Studies have also been conducted to determine whether these agents exhibit any detectable genotoxic effects on liver cells which would indicate that they are capable of initiating hepatocarcinogenesis. In the studies designed to detect the promoting potential of these agents, female Sprague-Dawley rats were partially hepatectomized and treated with DEN 24 hr later to initiate hepatocarcinogenesis. Twenty-four hr after injection the animals were transferred to diet containing the agent to be tested. In two separate experiments, animals were killed after 4, 9 and 12 mo of feeding diets containing the oral contraceptive steroids. Both intact animals and hepatocytes in primary culture were employed in studies designed to detect the ability of the oral contraceptive steroids to cause genetic damage in liver cells. Genotoxicity was assessed by using techniques to detect DNA damage either directly or indirectly. The results from all of these studies indicate the following: 1) mestranol and norethynodrel can promote DEN-initiated hepatocarcinogenesis as indicated by increased numbers of gamma-glutamyl transpeptidase positive, putative preneoplastic lesions after 4 and 9 mo and possibly adenomas and carcinomas after 12 mo; 2) mestranol appears to cause alterations in DNA as detected using alkaline elution; however, this is not reflected by the occurrence of detectable levels of DNA repair. (1 Ref)

26. THE MULTIPLE ROLES OF ESTROGEN IN ESTROGEN-DEPENDENT RENAL CLEAR-CELL CARCINOMA OF SYRIAN HAMSTER (MEETING ABSTRACT).

Liehr JG, DaGue BB, Ballatore AM, Sirbasku DA
Department of Biochemistry and Molecular Biology, University of Texas Medical School, Houston, TX, 77025
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Estrogen (estradiol [E2] or diethylstilbestrol [DES]), when implanted subcutaneously into male Syrian hamster, elicits renal clear-cell carcinoma after approx 6-8 mo. Estrogen alone causes this effect, ie no cocarcinogen is required for tumor initiation or growth response. Studies conducted in our laboratories and elsewhere indicate that the elevated level of estrogen in the hamster results in a variety of different responses and biochemical effects which in a concerted fashion lead to the phenomenon called renal clear-cell carcinoma. Tumor initiation by Estrogen: DES and E2 induce peroxidase activity and microsomal P450 enzymes in a variety of tissues. In turn, peroxidase and microsomal P450 enzymes oxidize DES to a quinoid structure. DES quinone, a chemically unstable and reactive substance, may spontaneously rearrange to beta-dienestrol or, in the vicinity of cellular macromolecules, may covalently bind to DNA. DES-DNA adduct formation was studied in vitro under various conditions. Estrogen Dependence of Tumor Growth: H301 tumor cells, which are derived from the estrogen-dependent renal clear-cell carcinoma of Syrian hamster, remain estrogen-dependent in culture or in host animals. Upon removal of the hormone implant, tumors immediately shrink in size and disappear within 10 days. Estrogen concentration in tumor tissue is low (12-30% of estrogen uptake of liver), despite the presence of estrogen receptors in tumor tissue. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

27. MODEL FOR HUMAN CARCINOGENESIS: ACTION OF ENVIRONMENTAL AGENTS (MEETING ABSTRACT).

Moolgavkar SH
Institute for Cancer Research, Philadelphia, PA
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Current statistical prescriptions for low-dosage extrapolation of carcinogenic risk make no distinction between exposure to initiators and exposure to promoters despite the abundant data that these two classes of carcinogens have different modes of action. One reason for this is the lack of an appropriate model. In this paper, a model for carcinogenesis is presented which provides a framework for understanding the roles of 'spontaneous' events, hereditary factors, and environmental agents in human carcinogenesis and for interpreting experimental carcinogenesis. This model incorporates two features: (1) transition of target stem cells into cancer cells via an intermediate stage in two irreversible steps, (2) growth and differentiation of normal target and intermediate cells. Cast in mathematical terms the model can be fitted to age-specific incidence data on human cancers of both children and adults and can illuminate the relative importance of agents that affect transition rates, tissue growth and tissue differentiation. Within the context of the model, initiators act by affecting the transition rates, whereas promoters influence the kinetics of growth, especially of initiated cells. The model provides a good quantitative description of the epidemiology of carcinomas of the breast and of the lung. The data are consistent with the notion that hormones and cigarette smoke act as promoting agents in carcinoma of the breast and of the lung respectively. (no Refs)

28. TUMOR PROMOTION AND PROSTAGLANDINS (MEETING ABSTRACT).

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International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The tumor promoters 12-O-tetradecanoylphorbol-13-acetate (TPA) and phenobarbital both appear us to induce the activity of rat hepatic ornithine decarboxylase (ODC). This induction is dose dependent, with an optimum dose at 20 ug -0.1 mg TPA per kg body wt and at 100 mg phenobarbital per kg body wt. The ODC activity has a maximal value at 4 hr after ip injection of the tumor promotor. It further is protein- and RNA-synthesis dependent. Treatment with retinyl-acetate one hr prior to TPA results in a dose dependent inhibition, being 85% at 20 mg per kg body wt, of the induce ODC activity. Retinyl-acetate at this dose fails to inhibit the phenobarbital induced activity. Analogical pretreatment with indomethacin shows an inhibition of the induced ODC activity, which raises the suggestion of the involvement of prostaglandins in the sequence of events from the application of the tumor promotor to the increase in activity of rat hepatic ornithine decarboxylase. Ip application of prostaglandins (PG E2 and PG F2alpha) both appear to inhibit ODC activity. These two observations possibly suggest a difference in mode of action between intra- and extracellular prostaglandins. (no Refs)

29. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

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Epidemiol Rev; 3:184-202 1981

Epidemiology of benign breast disease (BBD) is reviewed. Topics include BBD (the problem of case definition), estimates of the occurrence of BBD, evidence for an association of BBD and breast cancer, interaction of BBD and other risk factors for breast cancer, and factors associated with BBD (age, race, socioeconomic status, menstrual and reproductive characteristics, family history of breast cancer, obesity, endogenous hormone levels, and exogenous hormone use). Published data for the occurrence of BBD, risk of breast cancer associated with BBD, relative risk of breast cancer associated with various factors among women with and without BBD, menstrual and reproductive factors in relation to BBD, and biopsy-defined BBD and oral contraceptive use are summarized. Evidence suggests that risk of breast cancer associated with various factors may be greater in women with BBD than in those with no such history; inconsistencies across epidemiologic studies may result from a lack of analyses specific to histopathologic type of benign disease. (79 Refs)

30. EPIDEMIOLOGY OF PITUITARY ADENOMAS.

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Epidemiol Rev; 3:163-183 1981

Epidemiologic data, methodological problems associated with study of epidemiologic characteristics, and causal factors for pituitary adenomas are reviewed. Clinical features and treatment of pituitary adenomas are summarized. Incidence and prevalence are presented with respect to age, pituitary tumors in children and adolescents, time trends, sex differences, geographic variations, and multiple endocrine adenomatosis syndrome Type I. Exogenous risk factors presented are radiation, chemical carcinogens, estrogens, and oral contraceptives. Included are analyses of pituitary tumors as a proportion of all CNS neoplasms from selected studies, male:female ratios of incidence rates of pituitary tumors from selected reports, pituitary adenomas as a proportion of all primary CNS neoplasms from selected countries, av annual incidence rates/100,000 population for pituitary adenomas from selected countries, effects of diet, I131, and x-rays on induction of pituitary tumors in mice, incidence rate of pituitary tumors in female mice following total body neutron- and x-radiation, and frequency of pituitary adenomas in women with postpill vs non-postpill amenorrhea or amenorrhea-galactorrhea from selected reports. (154 Refs)

31. UTERINE LEIOMYOMATA: ETIOLOGY, SYMPTOMATOLOGY, AND MANAGEMENT.

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Fertil Steril; 36(4):433-445 1981

To improve understanding of the etiology and symptomatology of uterine leiomyomata, a review of literature is presented along with assessment of 4,714 myomectomies and records of 59 personal cases. Etiological consideration include histogenesis, estrogen, growth hormone, and progesterone. Symptomatology includes menorrhagia, infertility, pelvic pain and pressure, polycythemia, ascites, impingement, and related complications. The technique of myomectomy is dealt with in detail. A plan for management of uterine leiomyomata is presented for asymptomatic and symptomatic patients, both those desirous of fertility and those not desirous of fertility. (71 Refs)

32. CARCINOMA OF THE BREAST: PART 1, EPIDEMIOLOGY, SCREENING AND DIAGNOSIS.

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Md State Med J; 30(10):42-45 1981

It was estimated that 108,000 new cases of breast carcinoma will be diagnosed and 36,000 patients will die of this disease in the United States during 1980. Etiologic factors that have been claimed to influence breast cancer include: genetic and familial aspects, viruses (in some animal models), endocrine factors, reproductive function, estrogen and oral contraceptives, radiation, diet and obesity, trauma, and associated diseases such as extra-mammary cancer of fibrocystic disease. Screening for breast cancer may include mammography, thermography, and/or xerography in addition to physical examination and personal history. Brest cancer must be differentiated from other diseases of the breast including fibroadenomas, fibrocystic disease, acute or chronic mastitis, intraductal papilloma, Paget's disease or Mandor's disease. Diagnosis is by inspection, palpation and biopsy. Xeromammography is of great value in detecting an occult carcinoma of the breast and is also very useful in detecting a second primary carcinoma in the same breast or in the opposite one. Biopsy provides the definite diagnosis of breast cancer, but there is no evidence that mastectomy or a definitive procedure be done immediately and a few days delay does not seem to affect survival. (21 Refs)

33. IN VIVO ANALYSIS OF UV-B FORMATION OF 5-6 ALPHA EPOXY CHOLESTEROL (MEETING ABSTRACT).

Krinsky NI
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Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

To identify types of photooxidations initiated by UV-B in vivo, the cholesterol oxidation products formed when mice are irradiated with UV-B have been analyzed. Several compounds also have been prepared from 14C-cholesterol to serve as internal standards. Preliminary results indicate that cholesterol is the major radioactive skin steroid observed one hr after ip administration of mevalonic acid (MVA), with smaller amounts of two other radioactive compounds not yet firmly identified. For animals exposed to UV-B, increased amounts and types of more polar radioactive peaks have been found. Some observed changes may be due to UV-B catalyzed formation of vitamin D3 from 7-dehydrocholesterol. When cholesterol undergoes a Type I photooxidation, analogous to a radical oxidation, it forms the epimeric cholesterol 7-hyperoxides as well as the epimeric cholest-5-ene-3beta, 7-diols. In contradistinction, when cholesterol is oxidized by electronically excited (singlet) molecular oxygen in a Type II photooxidation, the initial product is 3beta-hydroxy-5-alpha cholest-6-ene-5-hydroperoxide. These compounds can be isolated and separated by thin-layer chromatography (TLC), by gas-liquid chromatography (GLC) and should be amenable to separation by high-performance liquid chromatography (HPLC). For max sensitivity, cholesterol labeled with either tritium (3H) or radioactive carbon (14C) will be utilized. The labeling will be carried out in vitro, using labeled mevalonic acid as a specific precursor of tissue cholesterol. Because mevalonic acid goes exclusively to steroids, this procedure avoids having large amounts of nonspecific radioactivity distributed through the tissues. Through the use of endogenous labeled cholesterol, the initial pathway of photooxidation induced by UV-B should be amenable to elucidation. Simultaneously, the formation of the carcinogen, cholesterol-5alpha, 6alpha epoxide will be followd by TLC and GLC and HPLC and attempts will be made to obtain precursor-product relationships in order to determine the immediate precursor of this compound. (no Refs)

34. THE INVOLVEMENT OF PROSTAGLANDIN INTERMEDIATES IN COVALENT BINDING TO NUCLEIC ACIDS AND IN AGEING PIGMENT FORMATION (MEETING ABSTRACT).

Vasdev S, O'Brien P
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International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Eling et al 1979 have shown that incubation of 1-C14 arachidonic acid with the microsomes of platelets, guinea pig lung, rabbit kidney and rat stomach fundus results in substantial binding to the protein. We also find that prostaglandin synthetase catalyzes the binding of arachidonate to exogenous DNA and RNA to form a fluorescent product. Prostaglandin could therefore play some role in carcinogene sis. The binding of prostaglandin intermediates to microsomal protein resulted in extensive crosslinking and polymerization of some proteins. This was prevented by glutathione or antioxidants and suggests that free radicals were involved. The formation of fluorescent products in the microsomes was attributed to conjugated schiff base product formation from the reaction between phospholipid amines and aldehyde. The spectra was similar to lipofuscin. In vivo lipofuscin pigment formation has been associated with aging, vitamin E deficiency, polyunsaturated fatty acid feeding and the ingestion of various environmental xenobiotics. The various tissues involved were lung, liver, heart, spleen, brain, kidney and testis. Incubation of the microsomes from these tissues with arachidonate resulted in protein polymerization and fluorescence formation. (no Refs)

35. IN-VIVO BROMOCRIPTINE EFFECTS ON PGE2 SYNTHESIS IN HUMAN PROSTATE (BPH AND PROSTATE CANCER) (MEETING ABSTRACT).

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International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The effects of bromocriptine (B) on human benign prostatic hypertrophy (BPH) have been investigated. A decrease in BPH-size was found in 15% of cases regardless of urodynamic status variations. By contrast, B was found to induce a marked urodynamic improvement in 77% of cases in a large series of patients (116 cases). This percentage declined to 68% in a single-blind, placebo controlled trial (SBP: 34 B vs 11 placebo patients) and 55% in a double-blind, placebo controlled trial (DBP: 40 randomized patients with 20 on B and 20 on placebo). The analysis of prostaglandin E2 (PGE2) content in urine suggested a close relationship between a lowering of PGE2 urinary levels and a positive urodynamic response to B, while PGE2 levels remained stable or increased when patients failed to benefit from B's course. It is suggested that rather than to be involved in the mechanism of action of B, PGE2 reflects the improvement of urinary outflow which appears to be achieved by the anti-adrenergic properties of the dopaminergic ergot derivatives. Surprisingly, an abnormally high incidence of prostate cancer was noted in patients who simultaneously failed to respond to B and whose PGE2 levels in urine remained stable or increased. These results will be discussed with respect to the hormonal status and risk of cancer of patients with uneasily slowing down PGE2 synthesis in prostate as well as in mammary gland. (no Refs)

36. CELL CYCLE ARREST POINTS IN NONTUMORIGENIC AND TUMORIGENIC CELL LINES, DEPENDENCY ON GROWTH FACTORS (MEETING ABSTRACT).

Meiss HK, Marcus M
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Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

We found that the ability of the TM4 cells to traverse G1 depends upon epidermal growth factor (EGF) more than upon insulin (ins) or transferrin (trf) as illustrated by the fact that in cultures starved for 3 days for EGF, 86% of the cells are arrested specifically in late G1, while omission of ins or trf for 3 days resulted in the arrest in G1 of only 61 and 75% of the cells, respectively. When the cells are starved for isoleucine or serum, 61% of TM4 cells are arrested in late G1. However, in presence of ins and trf, 0.3% serum supports growth. Therefore, 0.3% serum seems to provide what EGF provides. The tumorigenic derivative of TM4, designated TM4-T which cannot grow in serum free (sf) medium was also analyzed for its growth requirements. We found that more than 90% of these cells are arrested in G1 when starved for either serum or isoleucine. However, whereas TM4 cells under similar starvation conditions are arrested in late G1, TM4 cells are arrested in early G1. Hittelman and Rao have shown that in confluent cultures contact inhibited cells are arrested in early G1 while transformed cells under similar conditions are arrested in late G1. We found that the tumorigenic rat Sertoli cell line TRST is less dependent upon the growth factors than is the nontumorigenic line TM4. In cultures starved for 3 days for either EGF or trf only 61% of the cells are arrested in late G1, while in cultures starved for 3 days for ins the distribution of cells is similar to that in the random cultures. However, in TRST cultures starved for serum or isoleucine the fraction of arrested cells in late G1 is similar to starved TM4 cells. (1 Ref)

37. THE EFFECTS OF SODIUM BUTYRATE ON EPIDERMAL GROWTH FACTOR BINDING TO HUMAN COLORECTAL CANCER CELLS (MEETING ABSTRACT).

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Gastroenterology; 80(5,part2):1267 1981

Epidermal Growth Factor (EGF), a 6000 mol wt protein hormone produced by salivary and Brunner's glands, has been shown to have a mitogenic effect in normal intestine. Work in our laboratory has demonstrated that EGF stimulates the growth of human adenocarcinoma cells in culture as well as binding to a 180,000 mol wt cell surface receptor. Sodium butyrate (NaBt) has been reported to induce differentiation in some cancer cell systems. In this study a human rectal carcinoma cell line (HRT-18) and a human colon adenocarcinoma cell line (HT-29), whose growth is stimulated by EGF, were grown in the presence of NaBt to assess alterations in growth, tumorigenicity, EGF receptor numbers and characteristics. NaBt treated cells in both cell lines exhibited longer doubling times, lower saturation densities, and an inability to demonstrate anchorage independent growth when compared with control nontreated cells. A significant increase in receptor numbers was noted when expressed as binding per well or binding per mg protein. HRT-18 demonstrated a two-fold increase while HT-29 demonstrated a 1.3 fold increase after incubation with 2mM NaBt. This increase appears to require protein synthesis. Gel filtration and lectin affinity chromatography suggested that the EGF-receptor complex is a glycoprotein. In summary, NaBt can cause changes in cell growth in human colon cancer cells, suggesting lower tumorigenicity, while at the same time causing quantitative changes in EGF receptors. (no Refs)

38. PULMONARY METABOLISM OF PROSTAGLANDINS E2 AND F2ALPHA BY HAMSTERS TREATED WITH BENZO(A)PYRENE (MEETING ABSTRACT).

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Department of Pharmacologie, Universite Laval, Quebec City, Quebec, Canada

International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Benzo(a)pyrene is a potent pulmonary carcinogen. We hypothesized that the chronic exposition of the lung to this toxic agent produces alteration of the prostaglandin metabolism. This was tested by studying the biotransformation of the prostaglandin E2 and prostaglandin F2 alpha by perfused isolated hamster lung. During 15 wk, one group of animals received an intratracheal administration of a suspension of benzo(a)pyrene (3 mg) adsorbed to charcoal in saline; a second group received a charcoal saline suspension whereas only saline was administered to the third group. Prostaglandins and their metabolites were separated by thin-layer chromatography and quantified by liquid scintillation. In all groups the prostaglandins E2 and F2 alpha were respectively metabolized at 65% and 40%. The main metabolites were the 13-14 dihydro-15-keto PGE2 and the 13-14 dihydro-15-keto PGF2 alpha. The other metabolites were the 15-keto PGE2 the 15-keto PGF2 alpha. About 10 to 15% of the PGE2 and 20 at 25% of the PGF2 alpha were found after a first passage through the lung. In hamsters treated for 15 wk, benzo(a)pyrene produced morphological alterations of the lung structure and increased the lung wt. However, our results suggest that the pulmonary metabolism of prostaglandins E2 and F2 alpha is not altered in these animals. (no Refs)

39. MODULATION OF PROSTAGLANDINS IN HORMONE DEPENDENT MAMMARY CARCINOMA (MEETING ABSTRACT).

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International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Prostaglandin (PG) production may be hormonally modulated in hormone dependent mammary cancer. The purpose of this study was to relate the effects of in vivo hormone manipulations on tumor growth to accompanying changes in prostaglandin production. Mammary tumors were induced in female Sprague-Dawley rats by intubation of 5 mg of 7,12-dimethylbenz(a)anthracene (DMBA) at 4 weekly intervals. Prostaglandin production was measured as release of PG from tumor slices into an aqueous medium. PGs released into the medium increased with time up to one hr. The measurement of ng PG released/g tissue at 10 min was used for comparisons. Ovariectomy of tumor-bearing rats results in regression of the DMBA-induced mammary tumor 80-90% of the time. PGE2 production was increased 5-fold in regressing tumors compared to actively growing tumors. Non-regressing tumors from ovariectomized rats showed higher PGE2 production than growing tumors from intact rats, but not as high as the production in regressing tumors. 6-Ketoprostaglandin F1alpha release was measured to reflect prostacyclin production in the tumors. Production of 6-keto-PGF1alpha was elevated 2.5-fold in regressing tumors compared to growing tumors. The change in PG which is seen after hormone ablation suggests that PG production may be modulated by hormones such as estrogen, progesterone, and prolactin in the mammary tumors. (1 Ref)

40. PROSTAGLANDIN HYDROPEROXIDASE-MEDIATED 2-AMINO-4-(5-NITRO-2-FURYL)[14C]THIAZOLE METABOLISM AND NUCLEIC ACID BINDING.

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Cancer Res; 41(12):4961-4966 1981

Prostaglandin hydroperoxide-mediated metabolism and binding of 2-amino-4-(5-nitro-2-furyl)[14C]thiazole ([14C]ANFT) metabolite to nucleic acids and proteins were investigated with rabbit bladder transitional epithelial and solubilized ram seminal vesicle microsomes. Metabolism was assessed by spectrophotometric and radiochemical techniques. Substrate and inhibitor studies are consistent with both metabolism and binding of [14C]ANFT occurring by the prostaglandin hydroperoxidase activity of prostaglandin endoperoxide synthetase. The ratio of the rates of [14C]ANFT product formation is approx 3:7:10 (organic soluble:non-trichloroacetic acid precipitable: trichloroacetic acid precipitable) over a wide range of arachidonic acid concentrations. Approx 2 and 1% of the total [14C]ANFT metabolized binds to transfer RNA and DNA, respectively. The metabolite isolated from the organic phase had a chromatographic profile and UV spectra different from authentic ANFT. If transfer RNA or DNA is added at the end of a 5-min incubation, no binding to nucleic acids was observed. The demonstration of prostaglandin hydroperoxidase-mediated covalent binding to nucleic acids is consistent with the involvement of this enzyme in 5-nitrofuran-induced bladder carcinogenesis. (Author abstract) (44 Refs)

41. EFFECTS OF DEXAMETHASONE AND CORTISONE WITH X-RAY IRRADIATION ON TRANSFORMATION OF C3H 1OT1/2 CELLS.

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Nature; 293(5836):97-98 1981

It is reported that dexamethasone (DEX) and cortisone (CORT) do not suppress radiation transformation of C3H 1OT1/2 cells in vitro. DEX (10-7M) or CORT (10-7M) was added to the cultures immediately after irradiation (400 rad of x-rays) and subsequently added at each medium change for the 6-8-wk transformation assay. Dense cell foci were identified and scored as follows: Type 1 were abnormally dense but normal in other respects; Type 2 were large, moderately stellate, and tumorigenic in 60-75% of inoculated mice; and Type 3 were large, highly stellate, and tumorigenic in 80-100% of inoculated mice. The fraction of dishes used that contained Type 3 transformants was 0/40 for controls (no treatment), 12/77 for irradiation alone, 11/78 for CORT alone, 1/78 for DEX alone, 41/76 for irradiation and CORT, and 23/75 for irradiation and DEX. The fractions for cell Types 2 and 3 were 0.40, 26/77, 16/78, 3/78, 54/76, and 34/75, respectively. The results show that for cells exposed to both CORT and x-rays there seemed to be a synergistic response for the induction of malignant transformation. For DEX and x-rays, there was a higher yield of transformants than expected for an additive effect, but it was not significantly greater than the yield of transformants observed for radiation alone or for the expected additive effect of the combined treatments. It is speculated that when clinical efficacy is similar that DEX may give a decreased risk of tumor formation compared with CORT. (19 Refs)

42. THE ROLE OF THYROID HORMONE IN RADIATION AND CHEMICALLY INDUCED ONCOGENESIS (MEETING ABSTRACT).

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In Vitro; 17(3):203 1981

Neoplastic transformation in vitro by x-rays and chemical carcinogens has established the direct oncogenic potential of radiation and chemicals in mammalian cells. Little is known whether hormones, normally present in mammalian serum, can affect this response. Using short-term cultures of diploid hamster embryo cells, and the heteroploid mouse cell line C3H 10T1/2 we studied the effect of triiodothyronine (T3) on transformation. We have found that in both cell types the removal of thyroid hormone from serum-supplemented culture medium (using AG1-X10 resin) inhibits radiation and chemically induced transformation while having no effect on cellular growth rate or survival. When T3 alone is added to thyroid-depleted medium at 10(-7) M, transformation frequency induced by radiation is expressed at a similar frequency as in the presence of culture medium supplemented with untreated serum. We find that exposing the cells to T3 ranging from 10(-11) M to 10(-7) M results in radiation transformation which is dose dependent. Thyroid hormone is essential for the induction and/or expression of x-ray-induced transformations. Recent findings using Benzo-a-pyrene instead of x-rays as the oncogenic agent, indicate that in the absence of T3 there is no transformation and that T3 is required for the induction and/or expression of neoplastic transformation by the chemical carcinogen. (no Refs)

43. PROSTAGLANDIN SYNTHETASE CATALYZED DNA STRAND BREAKS BY AROMATIC AMINES (MEETING ABSTRACT).

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International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Several aromatic amines are renal medullary toxins and bladder carcinogens. We have found that the aromatic amines 2-naphthylamine, 2-4-diaminotoluene, p-aminophenol and p-phenetidine at a concentration of 50uM cause a 2-3 fold increase in DNA strand breaks in cultured human fibroblasts in the presence of sheep vesicular gland microsomes and arachidonic acid. Indomethacin and butylated hydroxyanisole inhibited this reaction. Curiously, benzidine did not give rise to a significant increase in DNA strand breaks. Metabolism of these amines by prostaglandin synthetase was judged by their ability to complete with and inhibit another prostaglandin synthetase dependent reaction - the activation of paracetamol. An 0.1 mM concentration of these amines inhibited the glutathione conjugate formation of paracetamol by 60-90%. Covalent protein binding of [3H]paracetamol was similarly inhibited. At the concentration used, these amines did not significantly affect the cyclooxygenase activity as judged by prostaglandin E2 and prostaglandin F2alpha formation. (2 Refs)

44. NEOPLASTIC TRANSFORMATION ASSAY WITH BALB/C 3T3 CELLS. ANALYSIS OF RESULTS WITH 70 CODED SAMPLES (MEETING ABSTRACT).

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Toxicologist; 1(1):131 1981

Exposure of certain populations of mouse BALB/c 3T3 cells to chemical carcinogens results in morphological transformation in the cell culture that can be identified and quantified. In the assay validation, 15 uncoded and 70 coded chemicals comprising a series of known carcinogens and noncarcinogens were tested using a standard protocol. Among the chemical classes tested, polycyclic aromatic hydrocarbons, direct-acting alkylating agents, activated aromatic amine metabolites and certain metal carcinogens gave positive responses. Aromatic amines, nitrosamines and other chemicals, such as natulan and cyclophosphamide, that require metabolic activation to exhibit activity, did not induce neoplastic transformation, although aniline was positive. The hormones ethynylestradiol, progesterone and diethylstilbesterol, which are likely epigenetic carcinogens, were not active in this system. Statistical analyses of the data reveal that: (1) the range of spontaneous transformation frequency has a mean value of 0.28 foci/plate; (2) the induced transformation frequency of the positive control (3-methylcholanthrene, 2 ug/ml) has a mean value of 2.6 foci/plate; (3) at control values above the cumulative mean, a doubling of transformation frequency in treated cultures is a statistically significant positive effect (alpha less than or equal to 0.05). At the control values below the cumulative mean, statistical significance is achieved only at higher treated to control response ratios, which rise sharply as control values approach zero. (4) The relationship of the untreated control response to the positive response is not a simple background incidence. (no Refs)

45. ORAL CONTRACEPTIVE EXPOSURE OF AMENORRHEIC WOMEN WITH AND WITHOUT PROLACTINOMAS.

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Int J Gynaecol Obstet; 19(5):381-387 1981

Extent of prior oral contraceptive (OC) used by women with prolactinomas is compared to that of other women with secondary amenorrhea. Ninety-three of 126 women with secondary hypothalamic-pituitary amenorrhea were evaluated for serum prolactin (PRL), by sella tomography, menstrual history, and OC usage and divided into three groups. Results for 26 patients (Group A) showed prolactinoma and hyperprolactinemia indicated by elevated PRL concentrations (greater than 30 nanog (ng)/ml) and radiographic abnormalities of sella turcica. Results for 26 additional patients (Group B) revealed idiopathic hyperprolactinemia only indicated by PRL levels greater than 30 ng/ml and normal tomographies of the sella. Forty-one patients (Group C) had normoprolactinemia indicated by PRL levels less than 20 ng/ml and normal tomographies of the sella. Duration of OC exposure ranged from none to greater than 12 mo. Evaluation for 'post pill amenorrhea' in OC exposed patients revealed 9, 11, and 15, in Groups A, B, and C, respectively. These proportions were not determined to be significant. The results suggest that nonovulatory patients are likely candidates for OC therapy. Patients with prolactinomas apparently do not differe in the extent of OC exposure from other specified groups of amenorrheic patients. (22 Refs)

46. MAMMARY-TUMOUR INCIDENCE IN SPRAGUE-DAWLEY RATS TREATED WITH 7,12-DIMETHYLBENZ(A)ANTHRACENE: EFFECT OF PREGNANCY AND LACK OF EFFECT OF UNILATERAL LACTATION.

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Br J Cancer; 44(3):451-455 1981

Mammary teat removal (thelectomy) was performed unilaterally in female Sprague-Dawley rats at 35 days of age. They were given 7,12-dimethylbenz(a)anthracene (DMBA) when aged either 55 days or 79 days. One third were unmated; one third were mated 1 wk and one third mated more than 3 wk after DMBA administration. Animals were killed when tumor-positive or after 1 yr, when mammary lesions had developed in 99% of rats. The mean latent period for adenocarcinomas was 18.9 +-2.0 wk. Benign mammary tumors, mainly secretory adenomas, developed significantly later (39.2 +-1.7 wk). The rapid unilateral involution of the thelectomized glands at parturition had no effect on the localization of either adenocarcinomas or benign mammary tumors. Pregnancy and delayed DMBA administration markedly reduced the incidence of adenocarcinomas; lactation had no significant effect. In a separate experiment, precocious puberty induced with pregnant-mare-serum gonadotrophin in 30-day-old female Sprague-Dawley rats enabled their first pregnancy and lactation to be completed by 80 days of age. Parity before carcinogen administration significantly delayed the development of adenocarcinomas. (Author abstract) (19 Refs)

47. PROSTAGLANDIN SYNTHETASE MEDIATED ACTIVATION OF P-DIMETHYLAMINOAZOBENZENE (BUTTER YELLOW) (MEETING ABSTRACT).

Vasdev S, Tsuruta Y, O'Brien P
Department of Biochemistry, Memorial University of Newfoundland, Newfoundland, Canada

International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The oral administration of dimethylaminoazobenzene (DAB) induces rodent liver tumors, mouse lung tumors and dog bladder tumors. It is believed that the activation by the liver of DAB involves liver microsomal mixed function catalyzed sequential N demethylation and N hydroxylation reactions. A cytosolic sulfotransferase then catalyzed the conjugation of the N-OH derivative with sulfate to form an electrophilic species which can bind to nucleic acids and protein. This electrophile is considered to be the ultimate carcinogenic metabolite. An alternative metabolic activation should now be considered. It has been found that prostaglandin synthetase can catalyze the binding of C14 DAB to microsomal protein. Extensive N demethylation occurred and C14 4-methylaminoazobenzene was much more effective at binding to the protein than DAB. Arachidonate was also more effective than NADPH with mouse lung and dog bladder microsomes. Cumene hydroperoxide was also much more effective than NADPH with rat liver microsomes. However, cytochrome P 450 was the catalyst for the latter hydroperoxide reaction as in this case extensive 4'hydroxylation also occurred. (no Refs)

48. SERUM-FREE GROWTH OF CHEF/18 AND MUTANT CELL LINES (MEETING ABSTRACT).

Sager R, Bennett F, Smith BL
Sidney Farber Cancer Institute, Boston, MA

Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

The growth factor requirements of non-tumorigenic cells grown for many passages in SF medium, and of transformed mutants and cell hybrids are correlated with their tumor forming ability. CHEF/18 cells maintain a growth rate indistinguishable from that in 10% serum (FBS) when grown for many passages in SF medium. However, cells round up and form tight balls resembling foci above the monolayer. Cells derived from foci do not clone in methylcellulose (MC) nor make tumors in nude mice. The foci arising in SF-medium do not form when thrombin or epidermal growth factor (EGF) is omitted from the medium, suggesting that either factor can induce similar reversible cytoskeletal and surface changes. Growth factor requirements were examined in a series of anchorage-independent (anch) and low serum (LS) mutants derived from CHEF/18 after mutagenesis with ethyl methane sulfonate or N-methyl-N'nitro-N-nitrosoganidine. The anch mutants require the same growth factors in SF-medium as the CHEF/18 parent. Although they clone well in MC medium + 10% serum, the anch mutants do not grow at all in SF MC medium. Similarly, the spontaneous low serum and anchorage-independent mutant CHEF/16, which is tumorigenic, and grows in SF medium does not clone in SF MC medium. Thus, the added growth factors lack some serum component required for anchorage free growth. Of the 12 mutants studied, 4 have a reduced insulin requirement. None of them have lost their EGF or thrombin requirements for SF growth and none have become tumorigenic. The correlation between loss of the EGF requirement and gain of tumor forming ability, previously proposed by Cherington et al is confirmed by the behavior of these mutants. Further confirmation of this correlation come from studies of cell hybrids formed by fusions between non-tumorigenic mutants derived from CHEF/18 and tumorigenic derivatives of CHEF/16. (no Refs)

49. STUDIES OF THE ENDOCRINE, PARACRINE AND AUTOCRINE CONTROL OF MAMMARY TUMOR CELL GROWTH (MEETING ABSTRACT).

Leland FE, Danielpour D, Sirbasku DA
Department of Biochemistry and Molecular Biology, The University of Texas Medical School, Houston, TX

Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Classical endocrine studies have shown that both estrogens and prolactin are required for growth of several types of carcinogen induced mammary tumors of experimental animals. However, despite the best efforts by many laboratories, the dramatic trophic effects of these hormones seen in vivo have been elusive in vitro. Our data, obtained with the MTW9/PL rat mammary tumor cell line, as well as data obtained by others with the MCF-7 and T47-D human mammary tumor lines, have shown that estrogens are required for optimum tumor formation by these cells in vivo, but either no or minimal mitogenic effects of estrogens are demonstrable in culture. To reconcile this observation, we have asked whether estrogen-regulated growth factors may be involved in mammary tumor growth in vivo. We have considered three possible mechanisms by which this process may occur: endocrine control; paracrine control; and autocrine control. We conclude from our studies that all three mechanisms may function in vivo, and that in addition, the differences between estrogen-responsive mammary tumor growth in vivo and autonomous growth in vivo may be related to the ability of the autonomous cells to produce paracrine/autocrine type growth factor constitutively. (no Refs)

50. GROWTH AND CLONING OF HUMAN SMALL CELL LUNG CANCER (SCLC) IN SERUM FREE, DEFINED MEDIUM (MEETING ABSTRACT).

Carney DN, Gazdar AF, Bunn PA, Oie H, Minna JD
National Cancer Institute, Washington, DC, 20422
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

A large number of continuously growing, tumorigenic, clonable cell lines of human SCLC have been developed which express a series of amine-precursor uptake decarboxylation (APUD) features and antigenic determinants recognized by SCLC specific monoclonal antibodies. The serum free growth factor requirements for mass culture replication of SCLC lines include medium RPMI-1640 supplemented with hydrocortisone, insulin, transferrin, estradiol, and selenium (HITES). We have applied this same formula to primary tumor biopsy specimens from SCLC patients and found that 77% of 38 tumor specimens grew in HITES medium as proved by cytology, nude mouse tumorigenicity, DNA content analysis, agarose clonogenicity, and APUD markers. This included samples from a variety of metastatic sites, and from untreated and relapsed patients. In contrast, patient specimens not involved with tumor or human tumors other than SCLC did not replicate in HITES medium. By 10 days, pure replicating populations of tumor cells free of stromal cells could be obtained. In fact, more tumor cell lines were started in liquid HITES medium than in serum containing medium. However, serum free conditioned medium from one SCLC line (NCI-N592) when added to HITES was found to stimulate the clonal growth in agarose to levels comparable to that seen in serum supplemented medium. This SCLC growth factor(s) is stable to freeze thawing, and boiling. We conclude, that SCLC cell lines and primary fresh tumors can replicate in defined medium, and that some SCLC lines produce a growth factor (s) which allows the clonal replication of SCLC in serum free medium. (3 Refs)

51. MODIFICATION OF BENZO(A)PYRENE-INDUCED CELLULAR TRANSFORMATION OF C3H/10T1/2 CELLS BY DEXAMETHASONE AND PREGNENOLONE-16ALPHA-CARBONITRILE (MEETING ABSTRACT).

Kuszynski G, Langenbach R
Eppley Cancer Institute, University of Nebraska Medical Center, Omaha, NE, 68105
In Vitro; 17(3):223 1981

Most chemical carcinogens exist in the environment in an unreactive form and require metabolic activation to exert their biological activity. Manipulation of the microsomal enzymes has been proposed as a mechanism for controlling carcinogenesis. In this study two compounds, dexamethasone (DEX) and pregnenolone-16alpha-carbonitrile (PCN), are potent inducers of microsomal enzymes in vivo. Since these enzymes are responsible for the metabolism of carcinogens, the effects of these compounds were studied to determine whether increased enzyme activity was correlated with cellular transformation. Both DEX and PCN were found to induce AHH activity in the C3H/10T1/2 cells by about 2 fold and both compounds increased the rate of metabolism of benzo(a)pyrene to water-soluble products. The steroids however had opposite effects on transformation. DEX inhibited cellular transformation by about 65% at 23 uM concentration. PCN, however, was found to increase the frequency of transformation by more than 100%. Therefore, enhanced AHH activity and metabolism does not necessarily lead to enhanced transformation since other pathways of metabolism, carcinogen detoxification, or repair processes may be involved. (no Refs)

52. BLOOD HORMONE PROFILES IN PROSTATE CANCER PATIENTS IN HIGH-RISK AND LOW-RISK POPULATIONS.

Ahluwalia B, Jackson MA, Jones GW, Williams AO, Rao MS, Rajguru S
Howard Univ. Coll. Medicine, Box 23, Washington, DC, 20059
Cancer; 48(10):2267-2273 1981

Epidemiologic data reveal that the incidence rate of prostate gland carcinoma among the black population in the United States (US) is several times higher than among Nigerians. A collaborative study between the two countries was undertaken, and blood hormone (testosterone [T], dihydrotestosterone [DHT], estrone [E1], estradiol [E2], and prolactin [P1]), total acid phosphatase (TP), and prostatic acid phosphatase (PAP) profiles in the two population groups were compared. In the US groups (patients and controls) there were significantly higher levels of T (p less than 0.01) and E1 (p less than 0.05) compared with the Nigerians. Also, the US patients had significantly higher levels of T (p less than 0.05) and E1 (p less than 0.01) compared with their matched controls. In the Nigerians T but not E1 levels were significantly lower (p less than 0.05) in patients compared with controls. DHT, E2, and P1 were not significantly different in patients and controls between and within the populations. Nigerian patients had higher levels (p less than 0.001) of TP and PAP compared with US patients. It is concluded that differences in blood hormone profiles in the two population groups are based on factors other than the genetic makeup of the populations. (Author abstract) (37 Refs)

53. PELIOSIS HEPATIS ASSOCIATED WITH CAVERNOUS HEMANGIOMA AND HEPATOCARCINOMA.

Herrera LO, Glassman CI, Teixido RA, Oglesby JT, Lopez Andrade E, Rodrigue RB
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Am Surg; 47(11):502-506 1981

Peliosis hepatis is a rare lesion characterized by blood-filled cavities randomly distributed in the liver. It has been associated with the administration of medications such as androgen-anabolic steroids, estrogens, oral contraceptives, and azathioprine. Its diagnosis is most reliably obtained by arteriogram and liver biopsy. Treatment consists of the discontinuance of those medications known to induce liver changes. Surgical treatment is reserved for those cases where a concomitant neoplasm or aneurysm is found. (Author abstract) (10 Refs)

54. RELATION BETWEEN ADRENAL FUNCTION AND 7,12-DIMETHYLBENZ[A]-ANTHRACENE-INDUCED MAMMARY CANCER OF THE RAT.

Nakamura Y, Kodama M, Kodama T
Dept. Surgery, Inst. Balneotherapeutics, Kyushu Univ., 4546 Tsurumihara, Beppu 874, Japan
Gan; 72(5):679-683 1981

The excretions of urinary steroids were investigated in rats in the course of mammary carcinogenesis by 7,12-dimethylbenz[a]anthracene (DMBA). The carcinogen was fed to female Sprague-Dawley rats on days 50 and 64 after birth at a dose of 10 mg each. The excretion of urinary androgen, 11-deoxy-17-oxosteroid (11-DOOS), increased temporarily (at 80 days of age) in DMBA-treated rats as compared with non-treated controls. The excretion of adrenal corticosteroid, 17-deoxy-corticosteroid (17-DOCS), was lower than normal in the rats that failed to develop tumors within 200 days after receiving DMBA. The difference between the above non-responders and the tumor-developing responders (or the non-treated controls) was significant at 80 and 120 days of age, but not at 160 days of age. The final tumors wt at 160 days of age were also positively correlated to the excretion of 17-DOCS at 130 days of age. It was indicated that the overall process of DMBA carcinogenesis could be promoted by the endogenous adrenocortical steroids. The possible mechanism underlying the production of mammary cancer is discussed in the light of the metabolic intimacy between DMBA and the adrenal steroids. (Author abstract) (17 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Abou-Issa H 39
Adams JB 12
Aflallo L 11
Ahluwalia B 52
Andersson B 43
Andolsek L 1
Arseneau JC 5
Ballatore AM 26
Bamji MS 20
Barrows GH 4
Bennett F 48
Bennett S 13
Besch NF 10
Besch PK 10
Bisschop A 28
Black AC 18
Borek C 42
Boynton AL 15
Brown CK 23
Buell RH 16
Bunn PA 50
Buttram VC 31
Carney DN 50
Casey HW 22
Christopherson 4
Concannon PW 22
Crowe N 23
DaGue BB 26
Danielpour D 49
Dao TL 7
Davis BB 40
Dufour M 38
Eisenburg J 3
Elias EG 32
Ernster VL 29
Feldman B 11
Foecking MK 39
Forsyth IA 46
Freeman L 9
Gazdar AF 50
Gingell R 19
Glassman CI 53
Glick SM 11
Gold EB 30
Goodrich-Smith 23
Guernsey DL 42
Hansel W 22
Hayden TJ 46
Healy GM 15
Herrera LO 53
Hertzog PJ 19
Huot J 38
Jackson MA 52
Jasberg K 21
Jiang NS 9
Jones GW 52
Jones JR 45
Kemmann E 45
Kennedy AR 41
Kim YS 37
Kodama M 54
Kodama T 54
Kovacic J 1
Kozuh M 1
Krinsky NI 33
Krishnamurthi D 20
Kuszynski G 51
Langenbach R 51
Latham KR 14
Lawson TA 19
Leland FE 49
Levy J 11
Liehr JG 26
Liel Y 11
Litt B 1
Lobb AM 44
Lopez Andrade E 53
Marcus M 36
Marshall W 13
Martin PM 35
Mattammal MB 40
Medline A 24
Meiss HK 36
Minna JD 50
Minton JP 39
Moldeus P 43
Moolgavkar SH 27
Moore BP 46
Mukundan MA 20
Nakamura Y 54
Nordenskjoeld M 43
Norwood PK 45
Nyby MD 21
O'Brien P 34
O'Brien P 47.
O'Brien PJ 13
Oglesby JT 53
Oie H 50
Ong A 42
Otubu A 10
Panganamala RV 39
Rahimtula A 43
Rajguru S 52
Rao MS 52
Reiter RC 31
Rodrigue RB 53
Rolland PH 35
Ross RK 8
Rudland PS 17
Sager R 48
Sandquist D 18
Schottenfeld D 2
Sellitti DF 14
Serment G 35
Sirbasku DA 26
Sirbasku DA 49
Sivak A 44
Smith BL 48
Sollars E 21
Sowers JR 21
Spraker TR 22
StHilaire RJ 37
Stevens SR 10
Sun AM 15
Teixido RA 53
Thibodeau SN 9
Thomas DB 6
Tremblay G 16
Tseng YC 14
Tsuruta Y 47
Tu AS 44
Tuck ML 21
Van Rooijen LA 28
Vasdev S 34
Vasdev S 47
Wanless IR 24
Warburton MJ 17
Weichselbaum RR 41
Welsch CW 23
Whitfield JF 15
Williams AO 52
Yager JD 25
Zenser TV 40

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Calabrese EJ

Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA

Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

2. RETROSPECT AND PROSPECT OF STUDIES ON DIGESTIVE SYSTEM DISEASES IN CHINA.

Zhang X

Dept. Internal Medicine, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Zhonghua Xiaohua Zazhi; 1(1):1-4 1981

In CHI

3. EPIDEMIOLOGY OF PITUITARY ADENOMAS.

Gold EB

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:163-183 1981

4. BLADDER CANCER EPIDEMIOLOGY.

Matanoski GM, Elliott EA

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:203-229 1981

5. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

Ernster VL

Dept. Epidemiology and International Health, 1699HSW, Univ. California, San Francisco, CA, 94143

Epidemiol Rev; 3:184-202 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

6. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R

Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany

Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

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7. CANCER AND THE PHYSICOCHEMICAL QUALITY OF DRINKING WATER IN QUEBEC.

Thouez JP, Beauchamp Y, Simard A

Dept. Geography, Univ. Montreal, Montreal, Quebec, Canada

Soc Sci Med [Med Geogr]; 15(1):213-223 1981

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8. ONCOGENIC VIRUSES.

Wyke JA

Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

J Pathol; 135(1):39-85 1981

9. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD

Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115

Haematol Blood Transfus; 26:483-487 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

10. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GENE-TOX PROGRAM.

Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Mutat Res; 87(2):143-188 1981

11. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.

Mohn GR

Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

Mutat Res; 87(2):191-210 1981

12. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.

Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E

Merck Inst. for Therapeutic Res., West Point, PA, 19486

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13. CANCER BIOLOGY.

Ruddon RW

Biological Markers Program, NCI-Frederick Cancer Res. Center, Frederick, MD

Cancer Biology. New York, Oxford University Press, 344 pp., 1981.

14. AVOIDABLE CANCER: ATTRIBUTION OF RISK.

Doll R

Radcliffe Infirmary, Oxford, England

S Afr Cancer Bull; 25(3):125-146 1981

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HORMONAL CARCINOGENESIS

SERIES CK05 No. 82/04

APRIL, 1982

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In this issue:

- **ORAL CONTRACEPTIVES AND HUMAN CANCER** 1-3
- **ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER** 4-5
- **MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES** 6-7
- **MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES** 8-9
- **HORMONAL CARCINOGENESIS IN ANIMALS** 10-11
- **REVIEWS AND OTHER RELATED STUDIES** 12-23

ORAL CONTRACEPTIVES AND HUMAN CANCER

1. ORAL CONTRACEPTION AND CANCER RISK.

Genton CY
Leitender Arzt, Abteilung fur Gynakopathologie, Institut fur Pathologie der Universitat, Universitatsspital, CH-8091 Zurich, Switzerland
Schweiz Med Wochenschr; 111(46):1742-1748 1981

Oral contraception was introduced 20 yr ago and is today the most popular method of preventing pregnancy. Some undesirable side effects of these drugs are well known, while others are only suspected. Many investigations have been undertaken to elucidate whether or not the Pill has carcinogenic properties, and the present study describes the current state of knowl-

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edge on this question. At present no evidence exists to suggest that oral contraceptives have carcinogenic effects on the human breast or genital organs. A causal relationship between use of these drugs and development of liver tumors is possible but far from proven. (Author abstract) (39 Refs) (In GER)

2. COLPOSCOPIC CHANGES INDUCED BY HORMONES.

Baader O
Freiburg, W. Germany
Arch Gynecol; 232(1):17-18 1981

The long-term follow-up of women using hormonal contraceptives by colposcopic photography showed no direct relationship between hormonal contraception and carcinogenesis. The hormonal effect was apparently restricted to the cervical mucosa. Reversibility of the hormonally induced changes was observed very soon after the cessation of the contraception. (no Refs) (In GER)

3. INCIDENCE OF OVARIAN CANCER IN RELATION TO THE USE OF ORAL CONTRACEPTIVES.

Weiss NS, Lyon JL, Liff JM, Vollmer WM, Daling JR
Dept. Epidemiology and Biostatistics, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Int J Cancer; 28(6):669-671 1981

Female residents of six counties in Washington and Utah in whom a diagnosis of ovarian cancer was made during 1975-79 were interviewed concerning prior use of oral contraceptives. Interviews with a random sample of women drawn from these same counties were obtained for comparison. A smaller proportion of women with epithelial ovarian tumors had taken oral contraceptives than had controls: the estimated risk of ovarian cancer in users relative to that in non-users was 0.57 ($p = 0.04$). The magnitude of the decreased risk depended on the duration over which oral contraceptives had been taken, as the negative association was present only after 4 or more yr of use. In many ways, the use of oral contraceptives mimics the physiologic effects of pregnancy. The results of the present investigation, when interpreted together with those from other epidemiologic studies and from experiments in animals, suggest that, like pregnancy, the use of oral contraceptives has a protective effect against the development of ovarian cancer. (Author abstract) (14 Refs)

ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER

4. EXOGENOUS ESTROGENS AND BREAST CANCER.

Lawson DH, Jick H, Hunter JR, Madsen S
(c/o Jick), Boston Collaborative Drug Surveillance Program, 400 Totten Pond Road, Waltham, MA, 02154
Am J Epidemiol; 114(5):710-713 1981

Rates of breast cancer at Group Health Cooperative of Puget Sound, Seattle, Washington, a health maintenance organization, remained stable from 1972-1979 in women aged 30-44 yr and in women aged 55-64 yr, despite the fact that the frequency of use of estrogen-containing drugs has varied substantially. By contrast, rates of breast cancer in women aged 45-54 yr appear to have fallen since 1977 in association with a substantial fall in estrogen use in women of this age group. The results are consistent with an etiologic role for current exogenous estrogen in breast cancer in middle-aged women. (Author abstract) (7 Refs)

5. ROLE OF HORMONES INCLUDING DIETHYLSTILBESTROL (DES) IN THE PATHOGENESIS OF CERVICAL AND VAGINAL INTRAEPITHELIAL NEOPLASIA.

Robboy SJ, Truslow GY, Anton J, Richart RM
Dept. Pathology, Massachusetts General Hosp., Boston, MA, 02114
Gynecol Oncol; 12(2,part2):S98-S110 1981

Current status of hormone usage and its relation to cervical neoplasia is reviewed. Analysis of neoplastic squamous cell lesions involving young women exposed prenatally to DES led to the definition of dysplasia and severe dysplasia and their separation from squamous dysplasia. Cytologic, histologic description, and correlation with DNA nuclear content are defined. Examination of DES-exposed women has shown discrepancies between cytology and biopsy specimens and possible intrinsic changes of the metaplastic and dysplastic cells. Comparison of rates of dysplasia in DES-exposed and nonexposed individuals within several yr will provide whether or not dysplasia occurs more frequently in DES-exposed women. Varied analysis of exposed and unexposed subjects disclosed that occurrence of dysplasia was more frequent in older subjects and in those who had intercourse with increased numbers of partners. Between the development of squamous cell carcinoma and DES exposure no link has been established. Recent studies have not resolved yet whether oral contraceptive agents play a causative role in the development of cervical neoplasia. Microglandular hyperplasia can also arise in young females exposed prenatally to DES. (48 Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES

6. ESTROGEN RECEPTOR QUANTITATION AND STAGING AS COMPLEMENTARY PROGNOSTIC INDICATORS IN BREAST CANCER: A STUDY OF 583 PATIENTS.

Godolphin W, Elwood JM, Spinelli JJ
Div. Clinical Chemistry, Vancouver General Hosp., Vancouver, B.C., Canada
Int J Cancer; 28(6):677-683 1981

Estrogen receptor (ER) quantity was measured at the time of primary diagnosis on 583 patients with breast cancer seen at the major treatment center in British Columbia between 1975 and 1979. Survival rates (overall, recurrence-free and post-recurrence) were assessed relative to ER concentration, staging, menopausal status, age, differentiation, and therapy. A linear trend in increased survival was demonstrable through variations in ER concentration from less than or equal to to greater than or equal to 260 fmoles/mg cytosol protein. This trend was highly significant and remained after adjustment for stage, menopausal status, and age, and was seen for all groups of patients except those with metastatic disease. The association of high ER concentration with increased recurrence-free survival was not due to differing response to adjuvant therapy, but the trend in post-recurrence survival was only significant in patients who had received hormonal therapy. Survival was as strongly associated with receptor concentration as with staging, and these two factors were almost completely independent. A proportional hazards model was fitted to produce predictions of survival, and showed that TNM Stage III patients with high ER concentrations have a better survival than Stage I or II patients with lower ER concentrations. This suggests that quantitative assessment of ER status is essential to definition of risk in breast cancer patients and that stratification in clinical trials and consideration for adjuvant therapy ought to be guided, in part, by a standardized ER-quantitative determination performed on the primary tumor. (Author abstract) (34 Refs)

7. CHANGES IN SEX STEROID HORMONE RECEPTORS IN RAT UTERINE CYTOSOL DURING EXPERIMENTAL INDUCTION OF ENDOMETRIAL CARCINOMA.

Nagasaka T
Dept. Obstetrics and Gynecology, Faculty Medicine, Univ. Tokyo, Bunkyo-ku, Tokyo 113, Japan
Nippon Sanka Fujinka Gakkai Zasshi; 33(6):757-766 1981

The sex steroid hormone receptor levels of uterine cytosol were assayed in the course of experimental induction of endometrial carcinoma in rats. The effects of administration of various hormones on the receptor levels were examined with each histological pattern of the endometrium. The dissociation constants for 17beta-estradiol and 17alpha,21-dimethyl-19-norpregna-4,9-diene-3,20-dione (R5020) binding with uterine cytosol were almost constant in spite of the various histological patterns of the endometrium. The influence of administered hormones on the receptor assay system could be counteracted by preincubation of uterine cytosol with dextran-coated charcoal 5x. Administration of diethylstilbestrol (DES) for 6 wk caused estrogen receptor levels to increase significantly in adenocarcinoma, while progesterone receptor levels did not show a tendency to decrease. Administration of mycophenolic acid (MPA) combined with DES did not cause a significant decrease in estrogen receptor levels in either atypical adenomatous hyperplasia or adenocarcinoma; progesterone receptor levels were decreased in all groups. Administration of MPA caused estrogen receptor levels to decrease significantly in adenocarcinoma. These data suggest that receptor levels can be controlled by the administration of sex hormones in the cause of development of endometrial carcinoma. (Author abstract) (36 Refs) (In JPN)

MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES

8. STUDIES ON THE MECHANISM OF CARCINOGENICITY OF DIETHYLSTILBESTROL: ROLE OF METABOLIC ACTIVATION.

Metzler M
Institut fur Pharmakologie und Toxikologie, Universitat Wurzburg, Versbacher Strasse 9, 8700 Wurzburg, W. Germany
Food Cosmet Toxicol; 19(5):611-615 1981

Oxidative metabolism of diethylstilbestrol (DES), meso-hexestrol (HES), and E,E- dienestrol (E,E-DIES) is reviewed. DES is metabolized to a variety of oxidative metabolites along several pathways involving reactive intermediates. This observation, together with evidence that DES also produces genetic damage, raises the possibility that metabolic activation may be involved in DES carcinogenicity. The mechanism for organ-specific carcinogenicity of DES may involve formation of reactive metabolites that retain their estrogenicity and are thus accumulated in estrogen target organs. A second possibility may involve the preferential formation of reactive metabolites in target organs by specific metabolites. Metabolic oxidation of HES is confined to the aromatic and aliphatic portions of the molecule. E,E-DIES is oxidized at the aromatic ring and at the olefinic double bond, and there is no indication of aliphatic hydroxylation. These analogues may be useful for further clarifying the role of metabolic activation in the genetic toxicity and carcinogenicity of DES. (34 Refs)

9. PROSTAGLANDINS AND CANCER: A REVIEW OF TUMOR INITIATION THROUGH TUMOR METASTASIS.

Honn KV, Bockman RS, Marnett LJ
Dept. Biological Sciences, Wayne State Univ., Detroit, MI, 48202
Prostaglandins; 21(5):833-864 1981

The role of prostaglandins (PG) in tumor initiation, promotion, and metastasis is reviewed. Results from tests in Salmonella typhimurium and mice suggest that prostaglandin endoperoxide synthetase (PES) may play a role in activating carcinogenic compounds, such as malondialdehyde, although findings may have been affected by carcinogenic impurities. Arachidonic acid may trigger cooxidation of noncarcinogens, such as benzo[a]pyrene to carcinogenic forms. The kidney may play a role in toxicity or carcinogenicity because of its physiological composition and high blood flow. PES appears to trigger carcinogens when introduced into dog kidneys in vivo. PG may play a role in tumor promotion by tetradecanoyl phorbol acetate (TPA). TPA treatments result in increased PG levels. Nontumorigenic phorbol esters do not increase PG levels. Some inhibitors of PES and lipoxygenases have been found to inhibit tumor growth in mice. PG apparently play a role in proliferation and differentiation of cells and therefore may affect tumor growth. PG appear to inhibit proliferation of monocyte and T lymphocyte precursors and to enhance proliferation of erythrocytes. Manipulation of PG levels may offer a means of controlling tumor growth and metastasis. (161 Refs)

HORMONAL CARCINOGENESIS IN ANIMALS

10. PROMOTING EFFECT OF TESTOSTERONE PROPRIONATE ON EXPERIMENTAL EXOCRINE PANCREATIC TUMORS BY 4-HYDROXYAMINOQUINOLINE 1-OXIDE IN RATS.

Hayashi Y, Katayama H
Div. Pathology, Natl. Inst. Hygienic Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158, Japan
Toxicol Lett; 9(4):349-354 1981

The promotion of 4-hydroxyaminoquinoline 1-oxide (HAQO) induced pancreatic tumors by androgenic hormone was tested in male and female rats. Three male (1m, 2m, and 3m) and three female groups (1f, 2f, and 3f) each consisting of 20 rats received 9 mg/kg iv injection of HAQO. Groups 1m and 1f received no further treatment. All other groups were castrated and subsequently given weekly sc injections of 1 mg testosterone propionate (groups 3m and 3f) or 0.1 ml olive oil (groups 2m and 2f). At 400 days the rats were autopsied and representative samples of pancreatic tumors were examined by electron microscopy. Eight exocrine adenomas of the pancreas developed in group 1m; six exocrine tumors developed in group 3m. One exocrine insuloma pancreatic tumor developed in group 1f and five were observed in group 3f. No exocrine adenomas of the pancreas developed in the control group or in groups 2m or 2f. Apparently testosterone can promote the induction of pancreatic tumors in rats by HAQO. (9 Refs)

11. LEUKEMOGENIC EFFECT OF URETHANE ADMINISTERED TOGETHER WITH ESTROGENS TO MICE.

Bojan F, Gomba Sz, Kertai P
Kozegeszsegtani es Jarvanytani Intezet, Debreceni Orvostudomanyi Egyetem, Debrecen, Hungary
Egeszsegtudomany; 25(3):251-255 1981

Effects of carcinogenic and noncarcinogenic substances administered together with estrogens or urethane were studied in 6-8-wk-old male CFLP mice. Each substance was administered in three individual doses during an 18-day period, and the results were evaluated after 300 days. Lung tumors and lymphomas were found in the animals treated with ethyl formate (500 mg/kg), phenylurethane (100 mg/kg), pyrene (5 mg/kg), and their combinations with diethylstilbestrol (DES: 25 mg/kg), but there was no significant difference in the percentage of tumor-bearing animals between the treated animals and the untreated controls. Other groups were treated with dimethylnitrosamine (10 mg/kg), benzo(a)pyrene (5 mg/kg), or 3-methylcholanthrene (5 mg/kg), or their combinations with DES. There was no significant difference in tumor frequency between the groups treated with the carcinogens only and those treated with the carcinogens and DES. Solid tumors in the abdominal cavity and hepatic tumor were also found in addition to lung tumors and lymphomas in the DES-treated groups. Other groups were treated with urethane with or without BCG or Escherichia coli endotoxin (ET): the carcinogenic effect of urethane was not modified by BCG and ET. In other experiments, urethane induced multiple lung tumors with and without DES, but the number of lymphomas was significantly higher in the group treated with urethane and DES than in the groups treated with urethane or DES alone. (24 Refs) (In HUN)

REVIEWS AND OTHER RELATED STUDIES

12. NUTRITION AND CANCER: A REVIEW.

Muller E, Rickenbach M
Institut fur Sozial- und Praventivmedizin, Universitat Zurich, Gloriastrasse 32 B, 8006 Zurich, Switzerland
Praxis; 70(43):1903-1912 1981

The possible roles of various nutrients in carcinogenesis are reviewed. Epidemiological studies indicate a high rate of carcinomas of the breast (BC) and colon (CC) in industrialized countries. Dietary factors are suggested by changes in cancer frequencies among immigrant populations and their descendants. Dietary studies indicate a positive correlation between dietary fat and CC and BC, as well as a negative correlation between these cancers and dietary fiber content. Animal studies have shown a cancer-promoting effect for fats, particularly unsaturated fats. Fats may promote cancer by affecting specific intestinal bacterial populations, bile secretion, hormonal balance, and immune response. Fiber may reduce cancer risk by speeding the movement of carcinogens through the digestive tract. Cancer risk has not been confirmed for proteins or their pyrolysis products. Some studies have indicated risk associated with pickled, smoked, or fried foods related to production of nitrosamines and nitrosamides. These compounds, which have been shown to be carcinogenic, are formed in vitro from nitrites and secondary amines. Their formation appears to be limited by the presence of ascorbic acid or vitamin E. Further studies of dietary factors are indicated. (130 Refs) (In GER)

13. SURVEILLANCE AND MANAGEMENT OF HEREDITARY BREAST CANCER.

Lynch HT, Albano WA, Organ CH, Schmitz GD, Lynch JF
Dept. Preventive Medicine/Public Health, Creighton Univ. Sch. Medicine, Omaha, NE
Breast; 7(4):2-9 1981

Clinical and biological characteristics of hereditary breast cancer are discussed to aid in establishing guidelines for its effective surveillance and management. Characteristics include significant early age of onset, excess of bilaterality and/or specific tumor associations, vertical transmission, and improved survival over nonhereditary forms. Recent observations suggest that a genetic linkage exists between breast cancer susceptibility and the glutamate-pyruvate transaminase locus in breast cancer prone families. Consistently lower plasma levels of prolactin, gonadotropin, estrone, and estradiol were measured in a high risk population, although the differences were not statistically significant. Oral contraceptives may act synergistically with other risk factors such as nutritional changes, alcohol usage, and increased cigarette smoking and may be primarily operative in familial breast cancer. Surveillance techniques include family counseling, monthly breast self-examination, biannual physician breast examination, mammography every 2 yr, and immediate biopsy of all dominant nodules. Existing breast cancers should receive standard evaluation and treatment, and the contralateral breast should be evaluated by mammogram and bio psy. The control of hereditary breast cancer could be aided immeasurably by the assembly of breast cancer prone kindreds in a carefully designed study. (35 Refs)

14. RISK FACTORS FOR BREAST CANCER: A TABULAR SUMMARY OF THE EPIDEMIOLOGICAL LITERATURE.

Kalache A
Dept. Community Medicine, Univ. Oxford, 8 Keble Road, Oxford OX1 3QN, England
Br J Surg; 68(11):797-799 1981

Nine categories of postulated risk factors for breast cancer and the approx relative risk for each factor are tabulated with key references. The categories are demographic, anthropometric, dietary, hormonal exposure, other exposure (ionizing radiation, drugs that increase prolactin secretion), and menstrual, reproductive, family, and past medical history. (38 Refs)

15. GENESIS AND PRECANCEROUS STAGES OF THE VARIOUS FORMS OF OVARIAN ADENOCARCINOMA.

Dallenbach FD
Heidelberg, W. Germany
Arch Gynecol; 232(1):33-35 1981

The genesis of ovarian adenocarcinoma is discussed. The risk factors include being single, hormonal disturbances, ovarian dysgenesis, hereditary predisposition, race, environment, diet, age, and preceding treatment with diethylstilbestrol. Adenocarcinoma develops from rests of the rete ovarii and from constricted inclusions of the superficial epithelium. A retrospective study of 80 patients with ovarian cystadenoma and adenocarcinoma revealed prior use of oral contraceptives (ovulation inhibitors) in 10/80 cases. (no Refs) (In GER)

16. BACKGROUND, DEVELOPMENT AND PROPERTIES OF PROGESTAGENS, WITH SPECIAL REFERENCE TO MEDROXYPROGESTERONE ACETATE (MPA).

Jeppsson S
Dept. Obstetrics and Gynecology, Malmo Allmanna Sjukhus, S--214 01 Malmo, Sweden
Acta Obstet Gynecol Scand [Suppl]; (101):7-10 1981

This review deals with the inhibitory effect of progestagens on pituitary gonadotropin release and endometrial proliferation and with the clinical use and side effects of 19-norsteroids and 17-OH-progesterone derivatives including medroxyprogesterone acetate. 17-OH-progesterone preparations are used without androgenic or estrogenic effects in the treatment of endometrial carcinoma; however, their use in oral contraceptives is no longer allowed in Sweden since they were found to increase mammary tumor incidence in beagles. (11 Refs)

17. EFFECTS OF DES ON THE MORPHOLOGY OF THE LOBES OF THE BABOON PROSTATE.

Chai LS, Karr JP, Murphy GP, Sandberg AA
(c/o Sandberg) Div. Medicine, Dept. Health, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Invest Urol; 19(3):202-208 1981

Ultrastructural examination of the baboon prostate has revealed differences between the caudal and cranial lobes. The cranial epithelium is characterized by electron dense, tall columnar cells which contain numerous secretory vacuoles of homogenous appearance; the caudal epithelium is comparativ ely shorter in height and lighter in electron opacity. The caudal cells also contain numerous secretory granules which vary in their characteristics. After diethylstilbestrol (DES) treatment (5 mg per day for 3 wk), the tall caudal cells were reduced to a cuboidal shape; the number of secretory granules in these cells was also markedly reduced. In the cranial lobe, cell height was only moderately reduced, but the secretory vacuoles were decreased both in size and number. In addition, the fibromuscular stroma of the cranial lobe was greatly expanded after DES treatment, with an increased distance between adjoining acini being clearly noted. The systemic effects of DES on the baboons were noted by significantly (p greater than 0.02) elevated levels of serum sex hormone binding globulin and significantly reduced serum testosterone levels (p less than 0.01). (Author abstract) (31 Refs)

18. ALTERATIONS IN GROWTH REQUIREMENTS OF KIDNEY EPITHELIAL CELLS IN DEFINED MEDIUM ASSOCIATED WITH MALIGNANT TRANSFORMATION.

Taub M, U B, Chuman L, Rindler MJ, Saier MH, Sato G
Biochemistry Dept., State Univ. New York at Buffalo, Buffalo, NY, 14214
J Supramol Struct Cell Biochem; 15(1):63-72 1981

Association of changes in growth requirements of kidney epithelial cells with malignant transformation was studied. Madin Darby Canine Kidney (MDKC) and baby mouse kidney (BMK) cell lines were cultured on Medium K-1 (serum-free medium supplemented with insulin, transferrin, prostaglandin E1 (PGE1), triiodothyronine (T3), and hydrocortisone). Both cell types grew on K-1 and responded to the individual supplements. Deletion of any single supplement resulted in decreased culture growth. The fewest MDKC or BMK colonies were found if transferrin or PGE1 was deleted. Results indicated MDKC as a suitable model for normal kidney cells in vitro. Malignant transformation of MDKC by Moloney sarcoma virus resulted in reduction of the optimal dose of insulin and the elimination in some cells of the PGE1 requirement. Transformed cells required fibronectin for growth in K-1. Variant cells were tumorigenic in adult nude mice and had altered cyclic AMP metabolism. (20 Refs)

19. THE LACK OF ESTROGEN CONTROL OF RODENT ALPHA-FETOPROTEIN LEVELS.

Sheehan DM, Branham WS
Div. Teratogenesis Res., Natl. Center for Toxicological Res., Jefferson, AZ, 72079
Teratogenesis Carcinog Mutagen; 1(4):383-388 1981

The possible regulation of alphafetoprotein (AFP) by estrogens was investigated. Diluted plasma from adult mice fed diethylstilbestrol, estradiol, or control chow did not display any high affinity binding of estradiol, but did show nonsaturable low-affinity binding attributable to albumin. Plasma from 15-day-old rats bound estradiol with a KD = 0.5 x 10(-8) M. Daily injection of estradiol did not alter the plasma decay curve of AFP. Dissociation constants did not change with age or treatment with estrogens. The failure of estradiol to alter AFP levels was not due to a lack of biologically effective estrogen since the neonatal uterus showed a significant wt gain response under the same conditions. It was concluded that estradiol does not alter existing AFP levels in the neonatal rat. (39 Refs)

20. INTERSPECIES RESPONSE TO CARCINOGENS AND OESTROGENS.

Drill VA
Dept. Pharmacology, Coll. Medicine, Univ. Illinois Medical Center, Chicago, IL, 60680
Food Cosmet Toxicol; 19(5):607-610 1981

The response of a range of species (mouse, rat, hamster, guinea pig, rabbit, dog, monkey, and man) to estrogens are contrasted with those to carcinogenic chemicals. The response to a carcinogen is a general biological response obtained in a variety of species; the carcinogen induces its specific neoplastic effect in a high proportion of treated animals in a relatively short period of time. Although estrogens may produce an organ-specific effect in mice or rats, they do not produce the interspecies effect characteristic of a carcinogen. Effects of estrogens are strain- and species-dependent and thus do not demonstrate a carcinogenic profile. When a positive response is obtained, only a small proportion of treated animals is affected. In addition, clinical data do not demonstrate a relationship between estrogen administration and the occurrence of breast or cervical cancer. Estrogens are best described as having a nonspecific permissive action. (30 Refs)

21. SYNTHESIS AND BODY DISTRIBUTION OF ALPHA-AMINOISOBUTYRIC ACID-L-11C IN NORMAL AND PROSTATE CANCER-BEARING RAT AFTER CHEMOTHERAPY.

Dunzendorfer U, Schmall B, Bigler RE, Zanzonico PB, Conti PS, Dahl JR, Kleinert E, Whitmore WF
Urologische Abteilung, Universitatskliniken Frankfurt, D-6000 Frankfurt/Main 70, W. Germany
Eur J Nucl Med; 6(11):535-538 1981

Alpha-aminoisobutyric acid-L-11C (11C-AIB) was synthesized and injected intracardially into healthy Copenhagen rats and into rats bearing transplantable hormone-sensitive or -insensitive prostate adenocarcinomas. Max 11C-AIB levels were found in the pancreas, spleen, and liver of healthy animals 45 min postinjection; prostate tumor concentration was significantly lower, but it was higher than the level in normal prostate. Stilbestrol treatment reduced the growth of hormone-sensitive tumors and also decreased tumor 11C-AIB levels. Effective chemotherapy with alpha-difluoromethylornithine and methylglyoxal bis(guanylhydrazone) decreased 11C-AIB levels in hormone-insensitive tumors. (9 Refs)

22. EFFECT OF MEDROXYPROGESTERONE ACETATE AND DOXORUBICIN ON SUBLINES OF 13762 MAMMARY ADENOCARCINOMA IN RATS.

Formelli F, Zaccheo T, Casazza AM, Bellini O, Di Marco A

Instituto Nazionale per lo Studio e la Cura Dei Tumori, Via Venezian, 1, 20133 M ilan, Italy

Eur J Cancer Clin Oncol; 17(11):1211-1221 1981

The 13762 mammary adenocarcinoma was subjected to serial transplantation in rats, freezing and thawing and in vitro cultivation. Following these procedures, various sublines were identified which differed in histological pattern, oncogenicity and sensitivity to medroxyprogesterone acetate treatment. Medroxyprogesterone acetate, administered sc at the dose of 100 mg/kg/day, 5 days/wk for 4 wk, delayed tumor onset and growth of sublines that had maintained their sensitivity to 17-beta-estradiol. Doxorubicin, administered iv at the dose of 3.6 mg/kg once a wk for 4 wk, was more active on the hormone-sensitive than on the hormone-insensitive subline. Simultaneous combined treatment for 4 wk with these agents caused higher growth inhibition than either single agent given alone. Other schedules of treatment were less effective. The following conclusions can be drawn: (1) the 13762 mammary tumor is heterogeneous, and hormone-sensitive or insensitive cell populations can be selected by simple manipulations; (2) there is no correlation between histological pattern and hormone sensitivity; (3) medroxyprogesterone acetate is active on sublines sensitive to 17-beta-estradiol treatment, but it also improves the activity of doxorubicin on hormone-insensitive sublines. (Author abstract) (22 Refs)

23. INFLUENCE OF PROLACTIN AND GROWTH HORMONE ON RAT MAMMARY TUMORS INDUCED BY N-NITROSOMETHYLUREA.

Rose DP, Noonan JJ

Div. Clinical Oncology, Wisconsin Clinical Cancer Center, Univ. Wisconsin, Madison, WI, 53792

Cancer Res; 42(1):35-38 1982

The effects of hypophysectomy and prolactin-suppressing drugs on the growth of mammary tumors induced in Sprague-Dawley rats by N-nitrosomethylurea and dimethylbenz(a)anthracene were compared. The influence of ovine prolactin and growth hormone administration on N-nitrosomethylurea-induced tumors was also studied in hypophysectomized animals. After hypophysectomy, all 13 tumors induced in 13 rats by N-nitrosomethylurea underwent regression, as did 10 of 12 induced by dimethylbenz(a)anthracene. There were no new tumors. Pergolide mesylate, a long-acting ergoline derivative, was given in a dose of 80 ug bid by sc injection for 28 days. Only 3 of 12 N-nitrosomethylurea-induced tumors regressed, while 4 became static. However, only two new tumors developed in the 12 pergolide-treated rats, compared to 11 in the 12 untreated controls. Bromocriptine mesylate, at 10x the pergolide dose, was even less effective; one of 16 tumors regressed, 2 became static, and 8 new tumors appeared in the 16 rats. In contrast, 8 of 12 dimethylbenz(a)anthracene-induced tumors regressed during pergolide therapy, 2 became static, and there was only 1 new tumor among the 12 rats. Prolactin, 1 mg bid for 7 days by sc injection, was given to another eight rats bearing 11 N-nitrosomethylurea-induced tumors, commencing 7 days after hypophysectomy. Regression of five tumors borne by four rats was reversed but resumed when treatment was stopped. Regression of five tumors in the other four animals was arrested without regrowth; the sixth became impalpable. All of these six grew rapidly when growth hormone, 2 mg bid, was administered in addition to prolactin. (Author abstract) (21 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Albano WA 13
Anton J 5
Baader O 2
Bellini O 22
Bigler RE 21
Bockman RS 9
Bojan F 11
Branham WS 19
Casazza AM 22
Chai LS 17
Chuman L 18
Conti PS 21
Dahl JR 21
Daling JR 3
Dallenbach FD 15
Di Marco A 22
Drill VA 20
Dunzendorfer U 21
Elwood JM 6
Formelli F 22
Genton CY 1
Godolphin W 6
Gomba Sz 11
Hayashi Y 10
Honn KV 9
Hunter JR 4
Jeppsson S 16
Jick H 4
Kalache A 14
Karr JP 17
Katayama H 10
Kertai P 11
Kleinert E 21
Lawson DH 4
Liff JM 3
Lynch HT 13
Lynch JF 13
Lyon JL 3
Madsen S 4
Marnett LJ 9
Metzler M 8
Muller E 12
Murphy GP 17
Nagasaka T 7
Noonan JJ 23
Organ CH 13
Richart RM 5
Rickenbach M 12
Rindler MJ 18
Robboy SJ 5
Rose DP 23
Saier MH 18
Sandberg AA 17
Sato G 18
Schmall B 21
Schmitz GD 13
Sheehan DM 19
Spinelli JJ 6
Taub M 18
Truslow GY 5
U B 18
Vollmer WM 3
Weiss NS 3
Whitmore WF 21
Zaccheo T 22
Zanzonico PB 21

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

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CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

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MODIFICATION OF CARCINOGENESIS

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Nasemann T
Univ.-Hautklinik Eppendorf, Martinistr. 52, D-2000 Hamburg 20, W. Germany
Hautarzt; 32(11):601-606 1981
In GER

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ICRDB CANCERGRAM

HORMONAL CARCINOGENESIS

SERIES CK05 No. 82/05

MAY, 1982

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In this issue:

- **ORAL CONTRACEPTIVES AND HUMAN CANCER.......... 1**
- **ORAL CONTRACEPTIVES AND HUMAN HEPATIC ADENOMA.......... 2-5**
- **ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER.......... 6-10**
- **MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES.......... 11-14**
- **MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES.......... 15-16**
- **HORMONAL CARCINOGENESIS IN ANIMALS.......... 17-19**
- **REVIEWS AND OTHER RELATED STUDIES.......... 20-36**

ORAL CONTRACEPTIVES AND HUMAN CANCER

1. DO ORAL CONTRACEPTIVES PREDISPOSE TO ENDOMETRIAL CARCINOMA? (MEETING ABSTRACT).

Gorstein F
No affiliation given
South Med J; 74(8):52P 1981

The possible relationship of oral contraceptive use to endometrial carcinoma has been the subject of considerable con-

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cern. The problem is a complex one due to the heterogeneous nature of the population, the variety of oral contraceptive agents, as well as the duration and mode of administration. However, since these agents have been in general use for approx 20 yr, meaningful data are now becoming available. Epidemiologic, morphologic, and pathophysiologic observations bearing on this question will be discussed. (no Refs)

ORAL CONTRACEPTIVES AND HUMAN HEPATIC ADENOMA

2. ORAL CONTRACEPTIVES AND HEPATOCELLULAR CARCINOMA.

Shar SR, Kew MC
(c/o Kew) Dept. Medicine, Univ. Witwatersrand, Medical Sch., Hospital Hill, Johannesburg 2001, South Africa
Cancer; 49(2):407-410 1982

A 23-yr-old woman was seen with an acute hemoperitoneum caused by rupture of a hepatocellular carcinoma. She died 2 yr after hepatic artery ligation. The patient had been taking oral contraceptives for periods of 1 yr and 10 mo, separated by a pregnancy. The association between oral contraceptive steroids and hepatocellular carcinoma is briefly reviewed. (Author abstract) (35 Refs)

3. HEPATIC LESIONS CAUSED BY ANABOLIC AND CONTRACEPTIVE STEROIDS.

Ishak KG
Dept. Hepatic Pathology, Armed Forces Inst. Pathology, Washington, DC
Semin Liver Dis; 1(2):116-128 1981

The pathobiology of hepatic lesions induced by long-term use of contraceptive (CS) or anabolic (AS) steroids is described. Lesions attributable to CS and AS may involve any of the systems of the liver, from the bile canaliculi to the hepatocyte to the vessels supplying and draining blood. Oral contraceptives have a number of physiologic effects upon the liver which include decreased bile flow, diminished secretion of organic anions and decreased synthesis and secretion of bile acids. Estrogens and progestins can increase the activity of many enzymes and alter the concentration of many plasma proteins. Subcellular alterations have been reported in humans and rats on AS and women on CS and involve multiple organelles of the several systems of the liver. Both AS and CS have been implicated in intrahepatic cholestasis, and in vascular complications including sinusoidal dilatation, peliosis hepatis, and Budd-Chiari syndrome. AS and CS have been associated with diffuse hyperplasia, nodular transformation, focal nodular hyperplasia, hepatocellular adenoma, hepatocellular carcinoma, and miscellaneous malignant tumors. Nonneoplastic effects include potentiation of preexisting liver disease, cholelithiasis, and pancreatitis. (167 Refs)

4. CONTRACEPTIVES AND THE LIVER.

Schmid M
Medizinische Klinik, Stadtspital Waid, Tiechestr. 99, CH-8037 Zurich, Switzerland
Leber Magen Darm; 11(5):216-226 1981

Studies on the relationships between the use of oral contraceptives (OC) and hepatic diseases are reviewed. The relationship between the long-term use of OC and benign hepatocellular adenoma is now beyond doubt. The progestagen component of the ovulation inhibitor acts as an enzyme inducer which may facilitate the formation of carcinogenic metabolites from various substances, and prompt elimination of these metabolites with the bile is prevented by the cholestatic effect of the estrogens. The relationship between OC and focal nodular hyperplasia is less evident. Here, the congenital hamartomatosis represents a site of least resistance for the hormones, but the steroid hormones are probably responsible for the vascular complications, especially for peliosis. Malignant hepatic tumors (hepatocellular carcinoma and especially hepatoblastoma and angiosarcoma) in connection with the long-term use of OC are extremely rare. The alpha-fetoprotein level is usually not increased significantly in patients with hepatocellular adenoma and carcinoma due to OC. (52 Refs) (In GER)

5. TOXIC AND METABOLIC LIVER INJURY.

Teschke R, Nishimura M, Gellert J
Medizinische Klinik D, Universitat Dusseldorf, Moorenstr. 5, D-4000 Dusseldorf, W. Germany
Leber Magen Darm; 11(5):227-234 1981

Studies on liver damage due to toxic substances and endogenous metabolites are reviewed. Liver cirrhosis due to phenylbutazone, dantrolen, diazepam, isoniazid, alpha-methyidopa, oxyphenisatin, azathioprin, mercaptopurine, methotrexate (MTX), and methyltestosterone was observed. Focal nodular hyperplasia due to oral contraceptives (ethinyl estradiol, mestranol, norethynodrel and norgestrel) was reported in the literature. These oral contraceptives, as well oxymetholone and methyltestosterone were found to induce hepatocellular adenoma. Hepatocellular carcinoma was found in patients treated with MTX, oral contraceptives, oxymetholone and methandrostenolone. (24 Refs) (In GER)

ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER

6. THE ROLE OF HORMONES IN THE ETIOLOGY AND PREVENTION OF BREAST CANCER AND ENDOMETRIAL CARCINOMA.

Gambrell RD
Dept. Endocrinology, Medical Coll. Georgia, Augusta, GA, 30912
Rev Bras Clin Ter; 10(9):671-678 1981

The roles of estrogens and progestogens in mammary and endometrial cancers were presented under the following headings: role of exogenous estrogens in endometrial cancer (EC), role of endogenous estrogens in EC, role of oral contraceptives (OCs) in EC, role of exogenous estrogens in mammary cancer (MC), role of endogenous estrogens in MC, and role OCs in MC. Administration of estrogen plus progestogen (EP) to menopausal women decreases the incidence of EC below that of untreated women. Postmenopausal women with increased endogenous estrogens should receive progestogens to reduce the risk of EC. OCs with EP in every tablet are protective against EC, while sequential administration provided less protection. MC is significantly less frequent in women receiving estrogens or EP than in postmenopausal women that never receive the hormones. OCs reduce the risk of benign mammary disease and give some protection against MC. Mortality rate due to MC is significantly lower in women who used OCs than in those who did not. (34 Refs) (In POR)

7. NONCONTRACEPTIVE ESTROGEN USE AND THE OCCURRENCE OF OVARIAN CANCER.

Weiss NS, Lyon JL, Krishnamurthy S, Dietert SE, Liff JM, Daling JR

Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104

JNCI; 68(1):95-98 1982

Female residents of six counties in Washington and Utah in whom ovarian cancer was diagnosed during 1975-79 were interviewed concerning prior use of noncontraceptive estrogens. Interviews with a random sample of women drawn from these counties were obtained for comparison. Taken as a whole, women with epithelial ovarian tumors reported estrogen use for 1 yr or more somewhat more often than did controls [relative risk (RR) = 1.3, 95% confidence interval (CI) = 0.9-1.8]. The proportion of women who had used estrogens varied according to the histology of their tumor, notably, of 17 women with endometrioid tumors, 12 had used estrogens (RR = 3.1, 95% CI = 1.0-9.8). the excess risk of endometrioid carcinoma related to estrogen use was not further increased when these hormones were taken for long durations, in high doses, or proximate to the time of diagnosis. Neither was there any evidence of increased risk from estrogen use in the small group of women with clear cell tumors, a histologic tumor type believed to be closely related to endometrioid carcinoma. Thus the observed association between menopausal estrogen use and the occurrence of ovarian endometrioid tumors should be interpreted cautiously until the results of additional studies are available. (Author abstract) (19 Refs)

8. AGE AT MENARCHE, PROBABILITY OF OVULATION AND BREAST CANCER RISK.

MacMahon B, Trichopoulos D, Brown J, Andersen AP, Aoki K, Cole P, DeWaard F, Kauraniemi T, Morgan RW, Purde M, Ravnihar B, Stormby N, Westlund K, Woo NC

Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA, 02115

Int J Cancer; 29(1):13-16 1982

An analysis is undertaken of the frequency of ovulation in 17 groups of women aged 15 to 19 who had been the subjects of other studies. A urine specimen of at least 8 hr accumulation had been provided on the 20th or 21st day of a menstrual cycle by 681 women. Analysis is restricted to 431 specimens which had been collected between 11 and 3 days prior to the onset of the subsequent menstrual period. A pregnanediol concentration of less than 1 mg/l in such a specimen was taken as evidence that the cycle was anovular. The probability of a cycle being anovular was inversely and significantly related to the number of yr since menarche, and, with yrs since menarche held constant, was positively but not significantly associated with age at menarche. This observation indicates that women with early menarche do not have a longer duration of exposure to anovular cycles than do those whose menarche is delayed, and that variation in the duration of exposure to post-menarcheal anovular cycles does not explain the association of breast cancer risk with early age at menarche. The 17 groups of women were classified into four categories according to ethnic origin and breast cancer incidence in the populations from which they derived. Anovular cycles were not more common in the high-risk groups; indeed, the two centers in the lowest risk category had the highest proportion of anovular cycles. (Author abstract) (15 Refs)

9. HORMONAL PATTERN AND SEX HORMONE BINDING GLOBULIN IN PLASMA OF WOMEN WITH CYSTIC BREAST DISEASE (MEETING ABSTRACT).

Berta L, Frairia R, Bumma C, Navello C, Mossetti C, Rovero E, Gaidano G

Patologia Speciale Medica B and Clinica Medica B, Univesita di Torino, Torino, Italy

International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

Fibrocystic mastopathy is a benign disease of fertile women, considered as a clinical condition at high risk for breast cancer. Etiopathogenesis is still uncertain but often the clinical onset has been related to plasma sex hormone imbalance. Sex Hormone Binding Globulin (SHBG) could be also involved. Recently SHBG has been hypothized to play a significant role in breast cancer development. The aim of present work was to study plasma hormonal pattern (E1; E2; P; prolactin, PRL) with respect to Sex Hormone Binding Globulin binding capacity (SHBG-bc) in fertile women with fibrocystic breast disease. In plasma of 57 women with fibrocystic breast disease (aged 18-42 yr) and of 30 normal control women (aged 21-45 yr) the following parameters have been evaluated: E1, E2, P, PRL by radioimmunoassay (RIA) (Biodata); SHBG-bc by an equilibrium partition technique (PEG/Dextran). All subjects were studied in the luteal phase of the menstrual cycle: they had body wt in normal range and were free from endocrinological, hepatic or renal diseases. Progesterone plasma levels significantly lower in patients than in controls are according to the data observed by Mauvais-Jarvis et al and confirm the hypothesis that altered ratio Estrogens/Progesterone interferes in the onset of the disease. Estradiol-17-beat and estrone plasma levels in our cases do not show significant difference, but SHBG-bc is lower in the patients than in normal subjects. These data support that Progesterone and SHBG-bc deficiency respectively induce a relative increase of estrogen plasma levels, influencing mammary epithelium proliferation. (no Refs)

10. HORMONE LEVELS IN HUMAN BREAST CYST FLUID (RELATIVE PLASMA CYST FLUID LEVELS) AND STUDIES ON THE MECHANISM OF ENTRY OF HORMONES INTO BREAST CYSTS (MEETING ABSTRACT).

Bradlow HL, Schwartz MK, Fleischer M, Rosenfeld SS, Kream J, Breed CN, Fracchia AA

Rockefeller University, Memorial Sloan-Kettering Cancer Center, New York, NY

International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

Cyst breast disease is a common occurence in women from age 35 to menopause. Alt hough breast cysts are not precancerous per se, repeated studies over many yr have reported and increased risk for breast cancer in women with breast cysts when compared to normal controls. As part of a program to explore the possible relationship between the unusual hormone levels found in breast cyst fluid and the incidence of breast cancer, the concentration of a wide variety of hormones in breast cyst fluid were determined and compared with the plasma levels of these same compounds. Hormone levels were measured in cyst fluid from 1046 women who were then followed to determine breast cancer incidence. Both peptide and steroid hormones were measured in cyst fluid and in blood samples obtained simultaneously. The peptide hormones measured were luteinizing hormone (LH), follicle stimulating hormone (FSH), human prolactin (HPrL) and beta human chor-

ionic gonadotropin (beta HCG). The first two compounds were present in cyst fluid in concentrations at or below plasma concentrations. HPrL and betaHCG however, were present in cyst fluid at concentrations greater than the plasma concentration in most of the patients studied. The cyst/plasma ratio ranged from only slightly greater than 1 to 200-fold. No correlation was found between the magnitude of the HPrL level and the betaHCG levels. The steroids studied were cortisol (F), testosterone (T), dihydrotestosterone (DHT), progesterone (P), estradiol (E2), estrone (E2), dehydroisoandrosterone (D), androsterone (A), and the sulfates of the latter four compounds. F, T, P. DHT, E1 and E2 were not significantly elevated in cyst fluid over plasma levels. D, A, DS, AS, E1S and E2S all showed elevated cyst fluid/plasma ratios, indeed in some cases as much as several thousand-fold greater than . Levels of DS and AS were as high as 20000 ug/dl. E1S and E2S were also markedly elevated in cyst fluid. (no Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES

11. MOLECULAR BASIS OF STEROID HORMONE ACTION IN BREAST CANCER AND ITS CLINICAL IMPLICATIONS.

Lunenfeld B, Geier A
Inst. Endocrinology, Chaim Sheba Medical Center, 52103 Tel-Hashomer, Israel
Isr J Med Sci; 17(9/10):954-959 1981

The measurement of steroid hormone receptors in tumors from patients with breast cancer is now established. Data have accumulated that seem to indicate that breast cancer patients may be selected for endocrine or adjuvant therapy on the basis of the presence or absence of estrogen receptors. Furthermore, patients without detectable estrogen receptors seem to have a greater likelihood of early recurrence following mastectomy. We describe recent findings on the mechanism of action of both estrogens and antiestrogens at the normal target cell level. Evidence for a similar mechanism of action for estrogens and antiestrogens in the hormone-responsive mammary tumor cell is presented on the basis of studies in hormone-dependent, dimethylbenz(a)anthracene-induced mammary carcinoma in the rat, and the cell line MCF-7 derived from a human breast carcinoma. The interaction of estrogens and antiestrogens with their receptors in the cytoplasm and nucleus in solid human breast tumors is discussed and analyzed in terms of the potential clinical application to breast cancer management. (Author abstract) (54 Refs)

12. STUDIES TO DETECT ESTROGEN RECEPTORS IN INTACT CELLS USING CYTOFLUOROMETRIC TECHNIQUES (MEETING ABSTRACT).

Tyrer HW, Pipho CJ, Mitra A, Oxenhandler R
Cancer Research Center, University of Missouri, Columbia, MO
VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire, Memorial Sloan-Kettering Cancer Center; 1981

We are developing assays to quantitate estrogen receptors in intact cells using a fluorescienated 17 beta-estradiol (17-FE). Although there is substantial physiologic and biochemical interest in studying estrogen binding reactions, 50-60% of mammary tumors with specific estrogen receptors respond to endocrine manipulations, whereas estrogen receptor negative tumors generally do not respond. Estrogen receptor studies using 3H-17-beta-estradiol and 17-FE have been performed in intact cells and cytosol of: 1) An estrogen receptor positive cell line derived from a rat pituitary tumor (GH3), 2) Estrogen negative cell line also derived from a rat pituitary tumor (RP2), and 3) Clinical samples obtained from the Ellis Fischel State Cancer Hospital. The 17-FE inhibits 17-beta-estradiol binding nearly as well as Diethyl stilbesterol, which is used for direct specific binding. Flow cytometry data follows the radiometric data. Cells from GH3 line show positive differences between total receptor fluorescence distribution and the non-specific receptor fluorescence distribution, whereas the RP2 lines show no differences. The differences between the distribution from GP3 cell lines correspond to about 60,000 receptors per cell. (no Refs)

13. INFLUENCE OF PRENATAL EXPOSURE TO DIETHYLSTILBESTROL ON ESTROGEN AND PROGESTIN BINDING PROTEINS IN UTERI AND DIMETHYLBENZANTHRACENE-INDUCED MAMMARY TUMORS OF THE RAT.

Heidemann PH, Wittliff JL, Calhoon RE, Boylan ES
(c/o Wittliff) Dept. Biochemistry, Health Sciences Center, Louisville, KY, 40292
J Toxicol Environ Health; 8(4):667-686 1981

Various characteristics of steroid binding proteins from mammary tumors and from uteri of rats exposed prenatally to diethylstilbestrol (DES) were examined. Pregnant rats were treated with no hormone (group A) or with a total dose of 1.2 ug DES during the second (group B) or third (group C) trimester of gestation. Female offspring received 7,12-dimethylbenz(a)anthracene (DMBA) at day 50 +-1. Animals with large mammary tumors were subjected to bilateral ovariectomy. The experiment was terminated 7 mo after carcinogen treatment. High-affinity binding sites for (3H)estradiol-17beta and (3H)R5020 were found in all mammary tumors assayed. Estrogen receptor forms 8S and 4S were identified on sucrose gradients of low ionic strength regardless of prenatal treatment. Progestin receptors (PR) sedimenting at 4S were also identified in the tumors. PR form 7-8S was found only in tumors from intact animals. PR levels diminished after ovariectomy in mammary tumors and in uteri. Uterine progestin binding capacities and uterine wet wt did not decrease proportionally after ovariectomy in group C. PR capacities in mammary tumors from group C were higher than in other groups. Cytosol from mammary tumors in group C intact rats also had elevated PR levels. Uterine estrogen binding capacities did not vary significantly. Prenatal exposure to DES during the third trimester appeared related to persistent biochemical alterations in rat mammary. tumors and uteri. Earlier exposure did not have the same effect. (61 Refs)

14. PEROXIDASE ACTIVITY AS A MARKER FOR ESTROGENICITY: STUDIES IN UTERUS AND MAMMARY TUMORS.

Levy J, Liel Y, Glick SM
Dept. Endocrinology, Soroka Medical Center, 84101 Beersheba, Israel
Isr J Med Sci; 17(9/10):970-975 1981

We examined the possibility that peroxidase activity might be a marker for estrogen activity in established estrogen-dependent tissues: dimethylbenz[a]anthracene (DMBA)-induced rat mammary tumors and human breast cancer. In DMBA-induced tumors undergoing regression after ovariectomy or tamoxifen treatment, tumor size decreased by 50%, estradiol receptors (ER) and progesterone receptors (PgR) decreased by 25 and 20%, respectively, but peroxidase activity paradoxically increased six- to sevenfold. In DMBA tumors stimulated by estradiol treatment or by the cessation of tamoxifen administration in intact rats, tumor size increased threefold. ER and PgR increased two- and threefold, respectively, while peroxidase activity decreased 50%. These data indicate an inverse relation between tumor growth, ER and PgR on the one hand, and peroxidase activity on the other. In the human breast cancers there was a significant negative relation between the presence of ER and peroxidase activity. By using a calibrated Sephadex G-100 column it was shown that uterine peroxidase differs in molecular weight from the peroxidase of rat mammary tumors and that of human breast cancer. (Author abstract) (21 Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES

15. STEROID HORMONE RECEPTORS AND PROSTAGLANDIN SYNTHESIS IN BENIGN BREAST DISEASES (MEETING ABSTRACT).

Rolland PH, Serment H, Martin PM

Laboratoire de Cancerologie Experimentale-Faculte Nord de Medecine, Clinique de Gynecologie-Obstetrique Hopital de la Conception, Marseille, France

International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

Studies on steroid receptor (SR) and prostaglandin (PG) synthesis in benign breast disease, from our viewpoint, are involved in further characterizing mechanisms of hormone cancerogenesis and tissular-hormone dependence of breast cancer in humans. Particularly, we have previously presented evidence suggesting that an elevated PG production is a marker of high metastatic potential for neoplastic mammary cells due to the improvement of the cellular autonomy which is concomitant to the loss of tissular-hormone dependence for these cells. When measured in both phases of the menstrual cycle of women suffering from benign mastopathies, plasma levels of both estradiol (E2) and progesterone (P) were lower in patients than in control women, resulting in an hormone imbalance with a relative excess of estrogen whose magnitude varies according to the individual degree of deficiency of P and E2. In both phases of the cycle, PGE blood levels were significantly higher in patients with benign mastopathies than in normal women. At the lesion's level, PG production was observed to be higher in benign disease than in normal breast. An estrogen-directed synthesis of PG is proposed to occur concomitantly to the benign epithelial hyperplasia induced by hormone imbalance. Similar results concerning estrogenic regulation of PG synthesis was observed in breast cancer. Both estrogen receptor (ER) presence and content increase as epithelial cell hyperplasia does in benign breast disease. A significant level of ER-PR couple appears in the lesions exhibiting lobular and ductal hyperplasia. Moreover, each lesion of high-intensity hyperplasia, ie diffuse ductal and lobular cell proliferation and hyperplasia associated or not with multiple papilomas, was found to be ER-PR positive while ER-PR couple was not detected in lesions in which fibrocystic alterations were associated with fibrosing adenosis. (no Refs)

16. THE HORMONAL PROFILES IN BREAST CANCER: A STIMULATING TOPIC (MEETING ABSTRACT).

Marangolo M, Fiorentini GM, Baccini C

Oncologia Medica and Laboratorio Analisi, Ospedale Civile-Ravenna, Italy

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer, 131 pp., 1981.

The identification of some 'risk factors' for breast cancer suggests the possibility that these women should be carriers of a subclinical pathological endocrinologic condition that acts as promoting factor in the incidence of mammary tumors; aim of this work is to verify this possibility. One hundred post-menopausal breast cancer patients (pts), all free of disease with early bone or skin metastases, were studied in control conditons and after Metopirone test, for determination of plasmatic Estrone (E1), Estradiol (E2) and Testosterone (T) over a period of 72 hr and with total 13 blood samples each patient. It was possible to identify a subgroup with concentrations of E2 equal or superior to the mean + 1 standard deviation (named Hyper-E2 : 14 patients) and a normal subgroup (86 pt) with values of E2 inferior to the Mean + SD for each sample. With statistical analysis it was possible to establish that Hyper-E2 pt were also Hyper-E1, on the contrary there was not statistical difference in the values of T between the two subgroups. The linear regression analysis showed no correlation, statistically significant, between T/E1 or E/E2 in both subgroups; a strong correlation became evident between T/E2 only in the Hyper-E2 patients. These data suggest the possibility that there exists a percentage of women with major capacity to aromatize the androgenic steroids in Estradiol. (no Refs)

HORMONAL CARCINOGENESIS IN ANIMALS

17. EFFECT OF SEX HORMONES ON PRODUCTION OF GASTRIC CARCINOMA (MEETING ABSTRACT).

Furukawa H, Iwanaga T, Ishikawa O, Fukuda I, Koyama H, Taniguchi K, Taniguchi H

Dept. Surgery, Center Adult Diseases, Osaka, Higashinari-ku, Osaka 537, Japan

Program and Abstracts of the 37th Meeting of Japanese Research Society for Gastric Cancer in Tokyo, 3 July, 1981. Japanese Research Society for Gastric Cancer, Tokyo 113, Japan, 6, 1981.

To determine whether or not sex hormones are related to carcinogenicity which differs in males and females, the following experiment was performed. Wistar rats were divided into four groups: Group 1, administration of 50 ug of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) per ml for 4 mo to male rats; Group 2, administration of 50 ug of MNNG per ml for 2 mo and subsequent sc injection of 400 ug of 17beta-estradiol (E2) per kg once a wk for 4 mo to male rats; Group 3, administration of 50 ug of MNNG per ml for 4 mo after male rats received orchiectomy; Group 4, administration of 50 ug of MNNG per ml for 4 mo to female rats. The rats were killed and examined 12 mo later. The incidence of gastric carcinoma after 12 mo from the beginning of the experiment in Groups 1, 2, 3 and 4 was 88%, 68%, 29% and 0%, respectively. Therefore, it was concluded that the injection of E2 and orchiectomy inhibited carcinogenesis. Rats in Groups 1, 2 and 4 were killed at the 4th, 6th, 8th and 10th mo. In Group 1, the incidence of carcinoma was 9%, 10%, 40% and 57% at the 4th, 6th, 8th and 10th mo, respectively: ie, the incidence of carcinoma increased with time. In Group 2, the incidence of carcinoma was lower than in Group 1, but the same tendency as in Group 1 was observed. In Group 4, hardly any carcinoma was observed. Changes in the gastric mucosa by erosion in the early stage in these three groups occurred in parallel with the incidence of gastric carcinoma at a high rate. Therefore, sex hormones are considered to have an effect on the incidence of carcinoma from the early stage. (no Refs) (In JPN)

18. EFFECT OF BOLANDIOL DIPROPIONATE (ANABIOL), AN ANABOLIC HORMONE, ON DIETHYLNITROSAMINE-INDUCED HEPATOCARCINOGENESIS IN RATS.

Mochizuki Y, Sawada N, Furukawa K

Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Nishi-17-chome, Minami-1-jo, Chuo-ku, Sapporo 060, Japan

Gan; 72(6):969-973 1981

The effect of bolandiol dipropionate (Anabiol), an anabolic steroid hormone, on hepatocarcinogenesis was investigated in rats. Anabiol was injected at a dose of 5 mg into the thigh muscle at intervals of 2 wk, simultaneously with or subsequently to the 4-wk administration of diethylnitrosamine (DEN). The average number of tumors larger than 3 mm in diameter per rat in the subsequently treated group at 25 wk after commencement of DEN was significantly increased and the number of tumors larger than 5 mm in diameter per rat in the simultaneously treated group was significantly increased, when compared with that in the group given DEN alone. Thus, the enhancing effect of Anabiol on hepatocarcinogenesis was evident in terms of tumor size, regardless of whether the hormone was given simultaneously with or subsequently to the carcinogen. (Author abstract) (24 Refs)

19. CANINE SCIRRHOUS GASTRIC CARCINOMA (MEETING ABSTRACT).

Miyasaka K, Kurihara M, Izumi T, Maruyama T, Sasaki Y, Yamatani F, Shirakabe H, Kamano T, Yasui A

Third Dept. Internal Medicine, Saitama Medical Sch., Moroyama-machi, Saitama Pref. 350-04, Japan

Program and Abstracts of the 37th Meeting of Japanese Research Society for Gastric Cancer in Tokyo, 3 July, 1981. Japanese Research Society for Gastric Cancer, Tokyo 113, Japan, 6, 1981.

Ten dogs were divided into three groups as follows: Group 1 (4 dogs), po administration of N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) (in food soaked with ENNG) for the first 4 mo and ENNG administration combined with sc injection of 5-10 gamma of gastrin per kg for the next 4 mo; Group 2 (3 dogs), administration of ENNG for 1 yr, but combined with sc injection of 5-10 gamma of gastrin per kg for 2 mo from the 5th mo of the administration of ENNG and for 6 mo from the 2nd mo from the end of the administration of ENNG; Group 3 (3 dogs), sc injection of 5-10 gamma of gastrin per kg for 7 mo after po administration of ENNG for 8 mo and then administration of serotonin for 8 mo. Scirrhous carcinoma with wall hypertrophy and stenosis on the pyloric antrum developed in one dog per group (a total of 3 dogs). The scirrhous carcinoma was histologically poor differentiated adenocarcinoma. Mucinous cells were observed in part of the carcinoma and infiltration into the serosa accompanied by marked proliferation of collagenic fibers was seen. It is suggested that the production of scirrhous gastric carcin oma involves gastrin. (no Refs) (In JPN)

REVIEWS AND OTHER RELATED STUDIES

20. AN EPIDEMIOLOGICAL BASIS FOR CANCER CONTROL.

Armstrong B

NH and MRC Res. Unit in Epidemiology and Preventive Medicine, Univ. Western Australia, Dept. Medicine, Nedlands, Australia

Cancer Forum; 5(3):136-143 1981

Primary and secondary prevention of cancer, particularly cancer of the lung, breast, and colon and melanoma, which together account for greater than 40% of new cancer cases and premature mortality is discussed. Primary prevention aims at preventing cancer from occuring by ending exposure to the causal agent either by environmental or life type control. Lung cancer is attributable mainly to cigarette smoking; some cases result from occupational exposure. Breast cancer is associated with nulliparity, first full-term pregnancy at a comparatively late age, low parity, diet, radiation, post-menopausal estrogens, and oral contraceptives. Colon and rectal cancer are mainly related to dietary fiber deficiency and excess fat and meat consumption. Melanoma of the skin is due to exposure to UV radiation. Etiologies of other neoplasms are discussed: brain neoplasms (phenobarbitone use), prostate cancer (diet, cadmium exposure), stomach cancer (diet), leukemia (x-rays, benzene exposure, antineoplastic agent use), pancreatic cancer (diet, cigarette smoking), bladder cancer (occupational exposure to aromatic amines, cigarette smoking), and cervix cancer (sexual promiscuity). Dietary modification, cessation of smoking, and avoidance of excessive exposure to UV light was recommended. Screening methods involved in the secondary prevention of cancer include cervical cytology, proctosigmoidoscopy, and mammography at regular intervals for certain segments of the population. The choice between primary and secondary prevention of cancer is discussed. (20 Refs)

21. WHAT DO WE KNOW ABOUT THE CAUSES OF OVARIAN CANCER?

Mount PM

Dept. Gynecologic and Breast Pathology, Armed Forces Inst. Pathology, Washington, DC

Contemp Obstet Gynecol; 18(6):47-49,53-54,58 1981

Current theories on initiation and growth of ovarian tumors are reviewed and interpreted. Ovarian cancer is the fourth most common fatal malignancy among women; modern diagnostic and treatment methods have had little impact on mortality. Epidemiologic studies have been impeded by a tendency to lump a multitude of histologic subtypes of ovarian cancer together, possibly masking important characteristics of particular types. Retrospective studies of risk factors for epithelial ovarian cancer have shown that the typical patient is either nulliparous or of low parity and has had difficulty in conceiving not attributable to anovulatory cycles. Long-term users of oral contraceptives appear to be at low risk for the disease. Theories of etiology are discussed. A simplified World Health Organization classification of the common epithelial tumors of the ovary is presented. Benign epithelial metaplasias are compared to their malignant counterparts. Genetic syndromes associated with ovarian neoplasms are reviewed. (20 Refs)

22. CANCER AND THE AGING PROCESS.

Morrison WB, Ott RL
Dept. Small Animal Medicine, Washington State Univ., Coll. Veterinary Medicine, Pullman, WA, 99164
Vet Clin North Am [Small Anim Pract]; 11(4):677-682 1981

Aging and the development of neoplastic disease in animals, including patterns of occurrence, the immune response, and the role of hormones are discussed. A variety of nonspecific irritative or inflammatory events exist that favor development of cancer by increasing the rate of cell division and probability for a mutation. Host DNA changes caused by chemical, viral, or physical agents also contribute to tumor evolution. The age-related incidence of cancer for a tumor type and species is reflected by the time necessary for these changes to become manifest in the host. (15 Refs)

23. PRIMARY HEPATIC CARCINOMA.

Iosquin CJ
Catedra de Medicina Interna A, Facultad de Ciencas Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981

Primary hepatic carcinoma (PHC) was reviewed. The following topics were discussed: etiology (cirrhosis, food, infections, parasites, hormones, thorotrast, As, and vinyl chloride), pathologic anatomy (tumors derived from the parenchyma or the mesenchyme), diagnosis (clinical, biological, and morphological), and treatment. (41 Refs) (In SPA)

24. ENDOCRINOLOGICAL ASPECTS OF BREAST PHYSIOLOGY (MEETING ABSTRACT).

Robyn C
Human Reproduction Research Unit, Universite Libre de Bruxelles, Hopital Saint-Pierre, Brussels, Belgium
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

Growth of the mammary gland is discontinuous; a first wave occurs at puberty under the influence of sex steroids, and the parenchymal breast tissue differentiates into a ductular-lobular-alveolar system. Growth slowly continues with each menstrual cycle up to the age of 30-35. A second major wave of growth takes place during pregnancy. Estrogens, progesterone and prolactin with variable relative potencies induce proliferation and differentiation of alveolar epithelial stem cells and control arborization of the ductular-lobular system. The interplay of the three hormones seems to be essential for optimal and balanced growth of the mammary tissue. From mid-pregnancy, the secretory differentiation of the alveolar stem cells is induced, predominantly under the influence of prolactin in synergism with metabolic hormones: this involves Messenger (m)-RNA synthesis for the production of milk proteins and enzymes. However, duri ng pregnancy most of the secretory effects of prolactin are suppressed and lactation does not occur: in vitro, progesterone suppresses the prolactin effects of casein m-RNA synthesis. After delivery, progesterone, estrogens and placental lactogen abruptly drop and prolactin induces full secretory activity and milk release. Oxytocin is required for milk ejection. Prolactin and oxytocin are released by neuroendocrine reflexes initiated by suckling. Prolactin does not appear to be essential for maintaining lactation. In mothers nursing for 2 yr or more, hyperprolactinemia persists for 15-18 mo; it is associated with infertility due to anovulation or corpus luteum deficiency. The decline in serum prolactin levels seen in the mothers after 18 mo of lactation is not associated with a decline in milk yield, at least when considering the amount of milk per feeding. Finally, the sequence of the endocrine events controlling full differentiation of the breast tissue and the timing of their occurrence seem to be of decisive importance in the resistance of the mammary epithelium to carcinogenic agents. (no Refs)

25. EFFECT OF AN LHRH ANALOG ON GROWTH AND HORMONE RECEPTOR LEVELS IN DMBA-INDUCED MAMMARY TUMORS IN THE RAT.

Turcot-Lemay L, Cusan L, Seguin C, Kelly P, Labrie F
Dept. Molecular Endocrinology, Le Centre Hospitalier de l'Universite Laval, Quebec G1V 4G2, Canada
J Recept Res; 2(2):135-151 1981

Hormone-dependency of dimethylbenz(a)anthracene (DMBA)-induced mammary tumors in rats was studied. Daily injections of luteinizing hormone-releasing hormone (LHRH) agonist, [D-Ala(6), des-Gly-NH2(10)]LHRH ethylamide (LHRH-A), 1 ug/day, for 38 days resulted in a 35% decrease in the number of tumors present at the start of the experiment compared to decreases of 45% after ovariectomy and of 8% in the control group. Although LHRH-A administration resulted first in a stabilization in the number of tumors, a marked inhibitory effect of the LHRH agonist on total tumor mass/rat was observed. There was marked reduction in ovarian luteinizing hormone (LH) and follicle-stimulating hormone (FSH) receptors while prolactin receptors were unchanged. Estrogen and progesterone receptor levels decreased after ovariectomy but treatment with LHRH-A had no significant effect on these receptors. Plasma LH and FSH levels increased after ovariectomy. Treatment with LHRH-A was followed by similar but less marked increases in plasma LH and FSH, with significant decrease in plasma prolactin and progesterone levels. The mechanisms by which LHRH-A induces the antitumor effect probably is related to desensitization of the ovary to LH and FSH with a concomitant decrease in circulating levels of estrogen and prolactin. (21 Refs)

26. HISTOLOGICAL EVIDENCE OF 'ESTROGENIC PROPERTIES' OF 7-12 DIMETHYLBENZ(A)ANTHRACENE.

Valero D, Drouhault R, Vanhems E, Bousquet J, Blanquet P
Unite 53, I.N.S.E.R.M., Domaine de Carreire, Rue Camille Saint-Saens, 33077 Bordeaux Cedex, France
Cell Mol Biol; 27(2/3):263-269 1981

DMBA (7,12-dimethylbenz(a)anthracene) and estradiol provoke in rat pituitaries an increase of prolactin cells number and of hormone synthesis. It is a transitory effect. Both enhance equally G6PD activity, this enzyme acting for an end product of a functional estradiol receptor. This increased reactivity persists during mammary tumor growth. These data added to previously published results, support the hypothesis that carcinogen would act in part by 'estrogen-mimetic' properties. (Author abstract) (25 Refs) (In FRE)

27. ELEVATED LEVELS OF ORNITHINE DECARBOXYLASE AND POLYAMINES IN THE KIDNEYS OF ESTRADIOL-TREATED MALE HAMSTERS.

Nawata H, Yamamoto RS, Poirier LA
Nutrition and Metabolism Section, Lab. Carcinogen Metabolism, NCI, Bethesda, MD, 20205
Carcinogenesis; 2(11):1207-1211 1981

The effects of 17 beta-estradiol (E2) on the levels of ornithine decarboxylase (ODC), S-adenosylmethionine decarboxylase

(SAMDC), and of the polyamines putrescine, spermidine and spermine in the kidneys of castrated male hamsters were determined. The ip injection of E2 into male hamsters led to renal ODC levels three times above the control levels 6-12 hr after treatment. Similarly, the renal ODC levels in hamsters treated with chronic doses of E2 for 60-180 days were 1.5-1.9 times the corresponding enzyme levels in control, sham-operated animals. With a series of estrogen analogues, there was a direct correlation between the rise in renal ODC in vivo and the binding to renal estradiol receptor sites in vitro. The hamster kidney levels of the polyamines putrescine, spermidine and spermine all declined during the 180-day experimental period. A single ip injection of E2 led to a 70% increase in renal SAMDC activity 12 hr after treatment. However, the administration of E2 for 180-270 days was without effect on the normal age-dependent decline in SAMDC levels noted in kidneys. These results indicate that, like other carcinogens and promoters, E2 increases the levels of ODC and of polyamines in its target tissue and that the rise in ODC is mediated by a specific estradiol-binding protein. (Author abstract) (30 Refs)

28. EFFECT OF NEONATAL CASTRATION ON LIVER TUMOR INDUCTION BY N-2-FLUORENYLACETAMIDE IN SUCKLING BALB/C MICE.

Toh YC
Dept. Physiology, Univ. New England, Armidale, New South Wales 2351, Australia
Carcinogenesis; 2(11):1219-1221 1981

BALB/c mice were castrated at 2 days of age and control animals were sham-operated. Untreated male and female mice were also included for comparison. One-half of the mice in each group were fed on alternate days with 1.5% N-2-fluorenylacetamide suspended in 1% gelatine by stomach tube beginning 1 wk of age for a total of 14 feedings. The experiment was terminated when the mice reached 1 yr old. Approx 30% of the male mice, but none of the females, developed liver tumors in groups fed carcinogen. This male predominance in the incidence of hepatocellular carcinomas was completely abolished when the animals were castrated neonatally. No lesions were observed in the liver of mice treated with gelatine suspension alone except one with neoplastic nodule. Although it has been observed that liver tumors are produced more readily in younger than in older mice, the present investigation shows that male hormonal environment during early life is more important than the age on the development of liver tumors initiated by carcinogen. (Author abstract) (21 Refs)

29. BREAST CANCER, FIBROCYSTIC MASTOPATHY AND HYPOTHYROIDISM: A CLINICAL CONTROVERSIAL PROBLEM (MEETING ABSTRACT).

Tarquini B, Benvenuti M, Bazzani M, De Cristofaro R, Taddei T, Santoro AC, Cagnoni M
Ist Clin Med II, Cattedra di Semeiotica Medica, Universita di Firenze, Florence, Italy
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

Clinical observations and available statistics indicate high rates (10 x) of breast cancer (BC) in hypothyroid patients. Nevertheless epidemiologic research suggests that hypothyroidism by itself does not show high potential malignancy. Moreover the role of thyroid gland remains a controversial problem despite of some decades of investigations. Also fibrocystic mastopathy (FM) is claimed to be a major risk factor in BC and it was found to be greatly increased in hypothyroid patients. Several risk factors have been shown to have combined effects in determining the lifetime probability of BC. In this view, we documented 4 women affected by BC (one bilateral) associated with FM and hypothyroidism. The role of thyroid hormones, as one of several sets of factors involved in mammary carcinogenesis, was reviewed with recognition of the fact that endocrine functions are usually rhythmic. (no Refs)

30. TURISTERON A NEW DRUG FOR ESTROGEN TREATMENT OF BREAST CANCER IN POSTMENOPAUSAL WOMEN (MEETING ABSTRACT).

Tanneberger S, Gurtler R, Bodek B, Morack G
Inst Cancer Research Acad Sci, Berlin, W. Germany
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer, 131 pp., 1981.

For the hormonal treatment of postmenopausal women at present diethylstilbestrol (DES) or Tamoxifen are available, both with comparable antineoplastic efficacy, tamxoifen with possibly somewhat less toxicity. Turisteron (Ethinylestradiolsulfonat) is a new oral depotestrogen with an av plasma elimination half-life of 6 days which has to be administered only once per wk. Forty patients treated wit h Turisteron were evaluated according to the World Health Organization criteria for response with the following findings: complete response (CR) 3/40, partial response (PR) 9/40, stable 20/40. Mean duration of response (min 3 mo) CR 27, PR 10, Stable 12 mo. The side effects were not higher than in a comparable group of patients treated with Tamoxifen. Due to the high antineoplastic efficacy of Turisteron achieved with the extremely simple schedule of once per wk administration. Turisteron seems to be a very promising palliative approach particularly for older women suffering from advanced breast cancer. (no Refs)

31. SELECTIVE EFFECT OF THE METALLOCARCINOGEN BERYLLIUM ON HORMONAL REGULATION OF GENE EXPRESSION IN CULTURED CELLS.

Perry ST, Kulkarni SB, Lee KL, Kenney FT
Univ. Tennessee-Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN, 37830
Cancer Res; 42(2):473-476 1982

Effects of the metallocarcinogen beryllium on regulation of gene expression were assessed by analysis of hormonal regulation of synthesis of tyrosine aminotransferase in beryllium-treated hepatoma cell cultures. Cell growth was not affected by exposure of the cells to 1 uM $BeSO_4$ throughout their 4-to 5-day growth cycle. In cells pretreated in this way, the induction by glucocorticoids was specifically impaired, the extent of induced enzyme synthesis being reduced about 50%. Inductions by insulin or cyclic adenosine 3':5'-monophosphate were not influenced by the metal. The results suggest that low concentrations of beryllium selectively interfere with regulatory mechanisms controlling transcriptional events in gene expression. (Author abstract) (24 Refs)

32. GENETIC EVIDENCE FOR MANY UNIQUE LIVER MICROSOMAL P-450-MEDIATED MONOOXYGENASE ACTIVITIES IN HETEROGENEIC STOCK MICE.

Lang MA, Gielen JE, Nebert DW
Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20205
J Biol Chem; 256(23):12068-12075 1981

Total cytochrome P-450 content, the Soret maximum of the reduced P-450-CO complex, NADPH-cytochrome c reductase activity, and 20 monooxygenase activities were determined in liver microsomes from each of 12 individual Heterogeneic Stock (HS) mice at varying times after 3-methylcholanthrene treatment. The choice of genetically very heterogeneous mice and the possibility of different turnover rates (synthesis/degradation) during the 3-methylcholanthrene induction process provided us with a strong likelihood of detecting differences in drug-metabolizing enzyme activities. Such diversity would also be expected among the human population. The substrates included benzo[a]pyrene, ethoxyresorufin, biphenyl, p-nitroanisole, 2-acetylaminofluorene, 7-ethoxycoumarin, zoxazolamine, estradiol-17beta, testosterone, progesterone, pregnenolone, dehydroepiandrosterone, and aldrin. By two-factor analysis of vari ance, 18 unique liver microsomal monooxygenase activities appear to be distinctly different from one another, out of the 20 activities chosen for study. Ethoxyresorufin O-deethylase activity is significantly correlated ($p = 0.11$) with aryl hydrocarbon (benzo[a]pyrene) hydroxylase activity. Dehydroepiandrosterone 16alpha-hydroxylase activity correlates well with the testosterone ($p = 0.33$), progesterone ($p = 0.16$), and pregnenolone ($p = 0.11$) 16alpha-hydroxylases. Testosterone 16alpha-hydroxylase, progesterone 16alpha-hydroxylase, and pregnenolone 16alpha-hydroxylase activities, on the other hand, are all significantly (p less than 0.001) different from one another. These data with intact microsomes illustrate the complexity of the problem with multiple P-450-mediated monooxygenases. Almost every activity therefore appears to be unique and probably reflects the aggregate contribution from numerous forms of P-450. (Author abstract) (33 Refs)

33. ENDOCRINOLOGIC ASPECTS OF BREAST CANCER RISK AND FIBROCYSTIC MASTOPATHY (MEETING ABSTRACT).

Tarquini B, Cecchettin M, Rosselli del Turco M, Cariddi A, Cavallini V, Nunnari G, Ciatto S
Ist Clin Med II, Cattedra di Semeiotica Medica, Univ Firenze, Florence, Italy
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

Fibrocystic disease of the human breast (FM) is obviously not a sufficient condition for the development of breast cancer (BC) because it is so common in comparison with the incidence of BC. Nevertheless FM is claimed to be a major risk factor involved in BC. A number of studies suggest that potential malignancy is related not only to histologic features but the other factors also intervene: 1) 14 women with histologically validated FM; 2) 14 women apparently healthy and without known risk factors (control groups); 3) 4 women with known FM and very high risk for BC. On each serum sample, Prolactin, thyroid stimulating hormone (TSH), luteinizing hormone (LH) follicle stimulating hormone (FSH), Gastrin, 17-beta-estradiol, Calcitonin and parathyroid hormone (PTH) were evaluated by radioimmunoassay kits. Each subject was sampled during the intermenstruum. Seven patients with FM and 7 controls were sampled 4 x in a yr with selection of the season of sampling. Some FM patients showed differences in serum levels of Prolactin, TSH, LH and PTH suggesting changes in combined risk. These results and related ethical problems in very high risk women are discussed. (no Refs)

34. GROWTH OF HUMAN BREAST CANCER IN A HUMAN TUMOR CLONING SYSTEM (MEETING ABSTRACT).

Von Hoff DD, Sandbach J, Osborne CK, Metelmann C, Clark GM
University of Texas Health Science Center at San Antonio, San Antonio, TX
Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussells, Belgium, European Organization for Research on Treatment of Cancer; 1981

A human tumor cloning system has been used to culture 431 patient's breast cancer specimens. Overall, in these 431 patients, 288 or 67% of their specimens formed greater than 5 colonies per 500,000 nucleated cells plated. Primary breast cancer constituted 260 of the samples. Of these, 188 (72%) grew (formed greater than 5 colonies/plated). The median colony count per plate was 47. There were 171 metastatic lesions cultured with 100 (58%) forming greater than 5 colonies per 500,000 nucleated cells plated. The median number of colonies per plate for metastatic lesions was 30. Growth from a variety of metastatic sites ranged from 22% for id lesions to 77% for solid visceral metastases. Methods to increase the number of colonies from a specimen including increasing the number of nucleated cells plated, using conditioned media from breast cancer cell lines and making a variety of changes in the growth media did not have a major impact on colony growth. Despite the difficulties with the cloning system it has been used to characterize the antitumor activity of standard anticancer agents (such as Adriamycin and medroxprogesterone) as well as explore the antitumor activity of two new anthracene derivatives, Mitoxantrone and bisantrene. Overall, the human tumor cloning system represents a new model for both basic and clinical studies of human breast cancer. (no Refs)

35. FECAL STEROID EXCRETION IN BENIGN BREAST DISEASE - SIMILARITIES TO BREAST CANCER (MEETING ABSTRACT).

Papatestas AE, Miller SR, Panveliwalla D, Aufses AH
Department of Surgery, Mount Sinai School of Medicine, New York, NY
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

The observed association between benign breast disease and breast cancer risk suggests a possible common etiologic mechanism. Fecal steroid levels have been linked to breast cancer risk through enhancement of estrogen synthesis from cholesterol metabolites. We have measured fecal steroids in women with breast cancer (cases) and in control women with or without benign breast disease (BBD). The former control group includes women with fibrocystic disease, intraductal papillomas, sclerosing adenosis and fibroadenomas. Three fecal specimens per patient were collected at the time of diagnosis and treatment, and the mean steroid value was evaluated. Determination of steroid levels in mg/g dry wt was made by the methods of Grundy and Miettinen. Comparison of the mean excretion of fecal steroids between controls with or without benign breast disease and cases, using analysis of variance showed significant differences for all neutral steroids but not for acidic steroids. The results indicate that women with benign breast disease have increa sed excretion of fecal steroids similar to that of cases but significantly higher than that of the remaining controls. T test for differences between groups (1) and (2) for total fecal steroids (TFS) equals p less than 0.01, for total neutral steroids (TNS) equals p less than 0.02, for first NS equals p less than 0.05, for second NS equals p less than 0.1. For total bile acids (TBA) there was no significant difference between groups (1) and (2). Women with fibrocystic disease did not seem to have high fecal steroids when compared to women with other types of benign breast lesions. Variations in degree of obesity between the three groups could not account for the observed differences as these persisted even among the subgroups of lean women. The findings support the concept of a common etiologic mechanism between benign and malignant breast lesions which seems to be linked to increased cholesterol synthesis and degradation in these two entities. (no Refs)

36. REGULATION BY STEROID HORMONES IN THE PROLIFERATION AND DIFFERENTIATION OF UTERINE ADENOCARCINOMA CELLS (MEETING ABSTRACT).

Nishiya I, Nunokawa S, Saito S, Miura T, Satoh M
Department of Obstetrics and Gynecology, Iwate Medical University, Morioka 020, Japan

VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire, Memorial Sloan-Kettering Cancer Center; 1981

In this paper, we describe some results which evaluated the influences of steroid hormones on cultured HeLa cells (originated from adenocarcinoma of the cervix) and SNG cells (established from human endometrial adenocarcinoma) by means of Laser-based flow microfluorometry (FMF), after quantitative fluorescent staining of mithramycin (MM) and propidium iodide (PI) with the treatment of DNase and RNase. Results obtained from the two kinds of adenocarcinoma cells in vitro are as follows: 1) Physiological relevant concentrations (5 x 10-8M). PI-fluorescnet intensity, after the treatment of RNase associated with nuclear DNA content, showed a remarkable increase in the S-phase cell population with addition of estrogens estradiol-17 beta, diethylstilbestrol and ethynyl estradiol. Progesterone followed a course similar to that of the estrogens. Upon measurement of MM-fluorescent intensity, patterns quite similar to the distribution curve of Pi-fluorescent intensity after RNase were obtained. 2) Therapeutic concentrations (5 x 10-5M, 5 x 10-6M). The addition of estradiol, diethylstilbestrol and ethynyl estradiol showed a loss of G2 peak and a difficulty of S-phase determination in both of PI-fluorescent intensity after RNase treatment and MM (in highest concentrations). The fact that Progesterone has an antagonistic effect on estrogen was found with the measurement of PI-fluorescent intensity after DNase treatment. Although priming effects by different steroid hormones are currently under investigation, a possible therapeutic implication of steroid effects upon uterine adenocarcinoma cells will be discussed. (no Refs)

☆ U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/118

AUTHOR INDEX WITH CITATION NUMBERS

Andersen AP 8
Aoki K. 8
Armstrong B. 20
Aufses AH 35
Baccini C. 16
Bazzani M. 29
Benvenuti M. 29
Berta L. 9
Blanquet P. 26
Bodek B. 30
Bousquet J. 26
Boylan ES 13
Bradlow HL 10
Breed CN 10
Brown J. 8
Bumma C. 9
Cagnoni M. 29
Calhoon RE 13
Cariddi A. 33
Cavallini V. 33
Cecchettin M. 33
Ciatto S. 33
Clark GM 34
Cole P. 8
Cusan L. 25
Daling JR 7
De Cristofaro R. 29
DeWaard F. 8
Dietert SE 7
Drouhault R. 26
Fiorentini GM 16
Fleischer M. 10
Fracchia AA 10
Frairia R. 9
Fukuda I. 17
Furukawa H. 17
Furukawa K. 18
Gaidano G. 9
Gambrell RD 6
Geier A. 11
Gellert J. 5
Gielen JE 32
Glick SM 14
Gorstein F. 1
Gurtler R. 30
Heidemann PH 13
Iosquin CJ 23
Ishak KG 3
Ishikawa O. 17
Iwanaga T. 17
Izumi T. 19
Kamano T. 19
Kauraniemi T. 8
Kelly P. 25
Kenney FT 31
Kew MC 2
Koyama H. 17
Kream J. 10
Krishnamurthy S. 7
Kulkarni SB 31
Kurihara M. 19
Labrie F. 25
Lang MA 32
Lee KL 31
Levy J. 14
Liel Y. 14
Liff JM 7
Lunenfeld B. 11
Lyon JL 7
MacMahon B. 8
Marangolo M. 16
Martin PM 15
Maruyama T. 19
Metelmann C. 34
Miller SR 35
Mitra A. 12
Miura T. 36
Miyasaka K. 19
Mochizuki Y. 18
Morack G. 30
Morgan RW 8
Morrison WB 22
Mossetti C. 9
Mount PM 21
Navello C. 9
Nawata H. 27
Nebert DW 32
Nishimura M. 5
Nishiya I. 36
Nunnari G. 33
Nunokawa S. 36
Osborne CK 34
Ott RL 22
Oxenhandler R. 12
Panveliwalla D. 35
Papatestas AE 35
Perry ST 31
Pipho CJ 12
Poirier LA 27
Purde M. 8
Ravnihar B. 8
Robyn C. 24
Rolland PH 15
Rosenfeld SS 10
Rosselli del Tu 33
Rovero E. 9
Saito S. 36
Sandbach J. 34
Santoro AC 29
Sasaki Y. 19
Satch M. 36
Sawada N. 18
Schmio M. 4
Schwartz MK 10
Seguin C. 25
Serment H. 15
Shar SR 2
Shirakabe H. 19
Stormby N. 8
Taddei T. 29
Taniguchi H. 17
Taniguchi K. 17
Tanneberger S. 30
Tarquini B. 29
Tarquini B. 33
Teschke R. 5
Toh YC 28
Trichopoulos D. 8
Turcot-Lemay L. 25
Tyrer HW 12
Valero D. 26
Vanhems E. 26
Von Hoff DD 34
Weiss NS 7
Westlund K. 8
Wittliff JL 13
Woo NC 8
Yamamoto RS 27
Yamatani F. 19
Yasui A. 19

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.
Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

DIETARY FACTORS IN CARCINOGENESIS

2. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.
Silverman J
American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

3. FORMATION OF N-NITROSO COMPOUNDS IN FOODS.
Gray JI
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
ACS Symp Ser; 174():165-180 1961

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

4. LYMPHOMAS AND LEUKAEMIAS. PART 2: TROPICAL AMERICA.
Jimenez E
Hospital Nacional de Ninos 'Dr. Carlos Saenz Herrera', Apartado 1654, San Jose, Costa Rica
Clin Haematol; 10(3):894-915 1981

5. LYMPHOMAS AND LEUKAEMIAS. PART 1: TROPICAL AFRICA.
Olweny CL
Uganda Cancer Inst., P.O. Box 3935, Kampala, Uganda
Clin Haematol; 10(3):873-893 1981

6. MALIGNANT MELANOMA.
Creagan ET
Div. Medical Oncology, Mayo Clinic, Rochester, MN, 55905
Compr Ther; 7(12):36-44 1981

7. MELANOTIC TUMORS OF THE UVEA AND RETINA.
Schmitt H
Universitats-Augenklinik, Theodor-Stern-Kai 7, D 6000 Frankfurt am Main, W. Germany
Med Klin; 76(24):672-675 1981
In GER

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

8. THE NATURAL HISTORY OF CARCINOGENESIS: IMPLICATIONS OF EXPERIMENTAL CARCINOGENESIS IN THE GENESIS OF HUMAN CANCER.
Pitot HC, Goldsworthy T, Moran S
McArdle Lab. for Cancer Res., Dept. Oncology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
J Supramol Struct Cell Biochem; 17(2):133-146 1981

9. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.
Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

10. BURKITT'S LYMPHOMA.
Ambrus JL, Ambrus CM
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Med; 12(6):385-413 1981

11. PRIMARY HEPATIC CARCINOMA.
Iosquin CJ
Catedra de Medicina Interna A, Facultad de Ciencas Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981
In SPA

METHODOLOGY IN CARCINOGENESIS RESEARCH

12. MUTAGENESIS AND CARCINOGENESIS TESTING IN VITRO.
Casto BC
Northrop Services, Incorporated, P.O. Box 12313, Research Triangle Park, NC, 27709
Biotechnol Bioeng; 23(12):2659-2671 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER IN THE YEAR 2000. A REVIEW.
Saxen E
Suomen Syoparekisteri, Liisankatu 21 B, 00170 Helsinki 17, Finland
Duodecim; 97(20):1708-1716 1981
In FIN

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ICRDB CANCERGRAM

HORMONAL CARCINOGENESIS

SERIES CK05 No. 82/06

JUNE, 1982

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In this issue:

- **ORAL CONTRACEPTIVES AND HUMAN CANCER** 1-3
- **ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER** 4-7
- **MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES** 8-12
- **MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES** 13-14
- **HORMONAL CARCINOGENESIS IN ANIMALS** 15-17
- **REVIEWS AND OTHER RELATED STUDIES** 18-28

ORAL CONTRACEPTIVES AND HUMAN CANCER

1. A REVIEW OF PROBLEMS OF BIAS AND CONFOUNDING IN EPIDEMIOLOGIC STUDIES OF CERVICAL NEOPLASIA AND ORAL CONTRACEPTIVE USE.

Swan SH, Petitti DB
(c/o Petitti) Dept. Medical Records Res., Kaiser-Permanente Medical Care Program, 3451 Piedmont Ave., Oakland, CA, 94611
Am J Epidemiol; 115(1):10-18 1982

Problems of bias (selection bias, errors of classification) and confounding variables that affect estimates of the relative risk of cervical neoplasia in users of oral contraceptives (OC) are

HE 20. 3173/2:

reviewed. Tabulated results of major epidemiologic studies of OC use and cervical neoplasia illustrate the extent to which the studies recognized and solved problems due to bias and confounding. (30 Refs)

2. PROTECTION AGAINST ENDOMETRIAL CARCINOMA BY COMBINATION-PRODUCT ORAL CONTRACEPTIVES.

Hulka BS, Chambless LE, Kaufman DG, Fowler WC, Greenberg BG
Dept. Epidemiology, Sch. Public Health, Univ. North Carolina, Chapel Hill, NC, 27514
JAMA; 247(4):475-477 1982

Seventy-nine patients with endometrial carcinoma were compared with 203 control subjects regarding their use of combination-product oral contraceptives (OCs). Overall, 6.3% of patients and 15.3% of control subjects had used these products. The risk of endometrial cancer for users of OCs was less than half the risk of nonusers. Five yr or more of use reduced the risk to a third. Recent users were strongly protected, whereas discontinuation resulted in risks returning to those of nonusers. Furthermore, OCs with predominantly progestational effects or intermediate formulations produced greater protection than those with predominantly estrogens. This pattern of results is biologically consistent with a protective effect of combination-product OCs against endometrial carcinoma. (Author abstract) (13 Refs)

3. ENDOMETRIAL CANCER, EPIDEMIOLOGY, AND MEDICAL PRACTICE.

Ryan KJ
Brigham and Women's Hosp., Boston, MA
JAMA; 247(4):496 1982

Recent findings that combination oral contraceptives (OC) reduce the risk of endometrial cancer in women reaching the age of 50 are critically reviewed. It is suggested that the risk of circulatory disease associated with the use of OC may outweigh the benefit of reduction of endometrial cancer. (3 Refs)

ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER

4. REPRODUCTIVE FUNCTION IN RELATION TO BREAST CANCER RISK.

Vorherr H
Dept. Obstetrics and Gynecology, Univ. New Mexico, Sch. Medicine, Albuquerque, NM
Excerpta Med Int Congr Ser; 551:224-233 1981

Factors which mediate breast cancer (BC) risk are discussed. While it has been reported that estrogens may decrease BC risk, in patients with estrogen-dependent BC they may accelerate malignant growth. While the proliferative action of estrone and estradiol have been linked to BC, the rise in BC incidence with advancing age parallels the gradual fall in estrogens. Estriol and 2-hydroxy-estrone protect the breast from estradiol-estrone hyperstimulation and carcinogenesis. Increased androgen conversion to estrone may stimulate epithelial proliferation of breast tissues toward overt carcinoma. Early menarche increases BC risk nearly twofold, while married women experience a twofold lower risk than unmarried women. Parous women have a two- to fourfold decrease in BC risk as compared to nonparous women. BC risk is increased in women undergoing late menopause. Bilateral ovariectomy before the age 40, early pregnancy, and extended lactation may protect against BC, while high parity coupled with early pregnancy, or late first pregnancy increase risk. (37 Refs)

5. HORMONAL GENESIS OF BREAST CANCER (MEETING ABSTRACT).

Mauvais-Jarvis P
Department of Reproductive Endocrinology, Hopital Necker, 75015 Paris, France
Third Meeting of the French Society of Senology and Mammary Pathology, October 15-17, 1981, Versailles. France Centre Rene Huguenin; 1981

This paper relates the different lectures given in December 9, 1980 by the speakers invited by the Breast Cancer Task Force Committee (Bethesda, MD) to participate in a workshop on luteal phase defects and breast cancer risks. The role of unopposed estrogen effect as a major promoting factor in human breast carcinogenesis is emphasized - particularly in terms of duration of exposure, especially during the first 'estrogen window' which precedes the first full term pregnancy. In the same conception, benign breast disease seems to be provoked by a progesterone insufficiency due either to the 'physiological' estrogen window occurring either after the beginning of breast development and during the perimenopausal period, or after stress exposure of women at any time of their reproductive life. In terms of prevention, the therapeutical use of progesterone and synthetic progestins in women presenting either a benign breast disease or a high risk of breast cancer is proposed in particular during the perimenarcheal period of the reproductive life. (no Refs)

6. BREAST CANCER RISK (MEETING ABSTRACT).

Sitruk-Ware R
Department of Reproductive Endocrinology, Hopital Necker, 75015 Paris, France
Third Meeting of the French Society of Senology and Mammary Pathology, October 15-17, 1981, Versailles, France Centre Rene Huguenin; 1981

Benign breast diseases (BBD) and breast cancer appear to have the same hormonal environment. Particularly, a long period of exposure to a high estrogenic activity without a proper secretion of progesterone, as during the perimenarcheal period, has been reported as one of the most important factors for the development of breast disorders. To analyze the risk of breast cancer according to the duration of this 'estrogen window' we decided to begin a large prospective study gathering large cohorts of patients in different French departments. A standardized questionnaire has been presented to the French cancerologists and gynecologists to enroll patients and controls in this study according to the same protocol. In this questionnaire we paid particular attention to the symptoms related to a hormonal disequilibrium, to the duration of the first estrogen window and to the use of contraceptive drugs during this period. (no Refs)

7. ETIOLOGICAL FACTORS IN MELANOMA.

Haim S, Gilhar A
No affiliation given
Harefuah; 101(5/6):125-126 1981

The etiology of melanoma is reviewed. Controversies involving theories which implicate exposure to UV radiation, skin color, atmospheric ozone levels, effects of sunlight on the immune system, and estrogen levels are discussed. (33 Refs) (In HEB)

MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES

8. ARE RECEPTORS MARKERS OF PRECANCEROUS DISEASE IN BENIGN BREAST LESIONS (MEETING ABSTRACT).

Concolino G, Marocchi A, Picardi C

University of Rome, Rome, Italy

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Eleven benign breast tumors (BBT) (fibroadenoma) were investigated for the presence of estradiol receptor (ER), progesterone receptor (PR) and androgen receptor (AR) both in the cytosol and in the nuclei of the cells, in order to get information on the possibility of malignant derangement of such lesions. The dextran-coated charcoal was rountinely employed: total ER were measured with the single step exchange-extraction with sodium thiocyanate, while PR and AR were measured using 3H-R5020 and 3H-R1881 with the addition of sodium molybdate. It was found that nuclear steroid receptors are present only in 27.3% of BBT (3/11), while the percentage of positive nuclear determinations for breast carcinoma was found to be 66.7%. ERc was present only in 3, while ERn was never detected in the 11 BBT studied. PRc was present in 6 and PRn in 2 of the 11 BBT examined. AR was the most frequently found, being present in the cytosol of 7 and only in 1 nuclear fraction of the BBT studied. We want to remark that BBT with only cytoplasmic receptors can be treated with hormone therapy, while BBT with cytoplasmic and nuclear receptors may be indicative of a 'high risk' of cancer and therefore should be treated with surgical removal of the tumor. (no Refs)

9. RETINOID BINDING IN NORMAL AND NEOPLASTIC MAMMARY TISSUE.

Moon RC, Mehta RG

Life Sciences Div., IIT Res. Inst., 10 West 35th St., Chicago, IL, 60616

Adv Exp Med Biol; 138:231-249 1982

Characterization of cytosolic retinoid binding proteins and nuclear translocation of cytosolic retinoic acid binding protein (cRABP) in mammary tissue during normal and neoplastic differentiation are reported. Relatively high levels of cRABP were observed in the mammary glands from pregnant animals as well as in ovarian hormone independent tumors; in glands obtained from lactating rats and in hormone dependent tumors, lower levels of cRABP were evident. Results indicate a possible correlation between endocrine and retinoid function in both normal and neoplastic differentiation of mammary tissue. A possible selective inhibition of ovarian hormone independent tumors by the retinoids is indicated. (52 Refs)

10. MAMMARY TUMOR INHIBITING EFFECT OF 3,3'-DIACETOXY-ALPHA,BETA-DIALKYLSTILBENES AND OF RELATED STILBENE OXIDES.

Schneider MR, Schonenberger H, Michel RT, Fortmeyer HP

Institut fur Pharmazie der Universitat Regensburg, Universitatsstrasse 31, D-840 0 Regensburg, W. Germany

J Med Chem; 25(2):141-145 1982

The compounds 3,3'-Diacetoxy-alpha,beta-dialkylstilbenes (alkyl = CH3 to C4H9, 1-4), 3,3'-dihydroxy-alpha,beta-diethylstilbene (5), and their corresponding oxides were synthesized. Compounds 1-10 competitively antagonized in vitro the interaction of [3H]estradiol with its receptor. 3,3'-Diacetoxy-alpha,beta-diethylstilbene (2), 3,3'-diacetoxy-alpha,beta-diethylstilbene oxide (7), and their phenolic analogues (5 and 10) were most effective. Shortening or lengthening the alkyl side chains led to a decrease in receptor affinity. Among the stilbenes and epoxides, those with C2H5 and C3H7 groups (2,3,5 and 7,8,10) caused the strongest inhibition of the growth of a hormone-dependent postmenopausal human mammary carcinoma serially implanted in nude mice. The strong antitumor activity of 5 and 10 was confirmed by experiments on the 9,10-dimethyl-1,2-benzanthracene-induced, hormone-dependent mammary carcinoma of the Sprague-Dawley rat. (Author abstract) (10 Refs)

11. STEROID RECEPTORS IN NORMAL HUMAN KIDNEY AND IN HUMAN RENAL CELL CARCINOMA (MEETING ABSTRACT).

Ronchi E, Veronese S, Cappelletti V, Di Fronzo G, Pizzocaro G, Piva L

Istituto Nazionale Tumori, Milan, Italy

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

The presence and quantity of cytoplasmatic androgen receptor (AR), estrogen receptor (ER) and progesterone receptor (PgR) have been studied in both cancerous tissue and surrounding normal parenchyma. To better characterize the specific steroid binding components and in order to discriminate between receptor proteins and steroid binding plasma proteins due to serum contamination of the tissue extracts, the cytosol were partially purified with protamine sulfate or by means of fractioned precipitation with ammonium sulfate at 35-50% of saturation. The binding kinetics were performed using the tritiated synthetic ligand methyltrienolone (R1881) for AR and 16alpha-ethyl-21-hydroxy-19-nor-4-pregnene-3,20-dione (ORG 2058) for PgR and 17 beta estradiol for ER either alone or in presence of 100 fold molar excess of unlabelled binding competitor R1181, ORG 2058 and diethylstilbestrol (DES) respectively. The separation of the bound from the free 3H ligand was obtained by DCC technique or gel filtration on Sephadex LH 20 in small disposable columns, and binding data plotted according to Scatchard's analysis. Of cancer patients so far investigated, 21% (12/57) were positive for AR, 12% (8/69) for ER and 10% (7/69) for PgR. The binding capacity of tumoral cytosol was found to be 8.60 fmoles/mg protein for AR, 4.11 fmoles/mg for ER, 3.32 fmoles/mg for PgR. In comparison to this value, the frequency of distribution of positive activity in normal kidney tissue were 18% (8/44) for AR 30% (18/56) for ER, 27% (15/56) for PgR with this av value: 6.00 fmoles/mg protien for AR, 3.84 for ER, 5.05 for PgR. The Ka of the binder-ligand complex from the cytoplasmatic fraction of tumors is essentially similar to that of normal kidney. (no Refs)

12. PROLACTIN AND PROLACTIN RECEPTOR INTERACTIONS IN NORMAL AND NEOPLASTIC TISSUE.

Kelly PA, Djiane J, Turcot-Lemay L
Dept. Molecular Endocrinology, Le Centre Hospitalier de l'Universite Laval, Quebec G1V 4G2, Canada
Adv Exp Med Biol; 138:211-229 1982

Regulation of hormone receptors in nitroso-methylurea (NMU)-induced mammary tumors, the interaction of prolactin with prolactin receptors, and the down-regulation of prolactin receptors induced by prolactin both in vivo and in vitro are described. Prolactin receptors in NMU-induced tumors are reduced following ovariectomy of animals with newly formed tumors (2.5 mo after NMU injection) or in those animals with tumors present for longer periods. Prolactin receptors appear to have a relatively rapid turnover, based on the rate of receptor replenishment following removal of cycloheximide. (50 Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES

13. INHIBITION OF ESTROGEN BIOSYNTHESIS AND REGRESSION OF MAMMARY TUMORS BY AROMATASE INHIBITORS.

Brodie AM, Brodie HJ, Romanoff L, Williams JG, Williams KI, Wu JT
Worcester Foundation for Exerimental Biology, Shrewsbury, MA, 01545
Adv Exp Med Biol; 138:179-190 1982

Inhibition of estrogen biosynthesis and regression of mammary tumors by aromatase inhibitors (AI) were studied in vitro utilizing the human placental and pregnant mares' serum gonadotropin (PMSG)-primed rat ovarian microsomal system. Compounds studied were 4-hydroxyandrostene-3,17-dione, 4-acetoxyandrostene-3,17-dione, and 1,4,6-androstratriene-3,17-dione. Effects of AI on mammary tumors were also studied and metabolic studies with AI conducted. (27 Refs)

14. ARACHIDONIC ACID TRANSFORMATION AND TUMOR PRODUCTION.

Levine L
Dept. Biochemistry, Brandeis Univ., Waltham, MA, 02254
Adv Cancer Res; 35:49-79 1981

The relationship between arachidonic acid (AA) and cancer is reviewed. Biochemical pathways of AA leading to endoperoxides and several substrates of the lipoxygenases are presented, and prostaglandin (PG) levels in tumors are discussed. AA transformation in relation to hypercalcemia and tumor production is reviewed. Discussion includes the effects of 12-O-tetradecanoyl phorbol-13-acetate (TPA) on PG production of cells in vitro and in vivo and the effect of inhibitors of PG production on TPA activity in cultured cells. Stimulation of PG production by growth factors, the effects of PG on cell or tumor growth, and the relationship between PG and immune response are reviewed. Acylhydrolase activity , or possibly cylooxygenase activity, is more likely than lipoxygenase activity to be causally related to cancer. Future studies concentrating on the mechanism of inhibition of acylhydrolase activity may be important for control of tumor growth. (209 Refs)

HORMONAL CARCINOGENESIS IN ANIMALS

15. ETIOLOGY OF DES-INDUCED UTERINE TUMORS IN THE SYRIAN HAMSTER.

Leavitt WW, Evans RW, Hendry WJ
Worcester Foundation for Experimental Biology, Shrewsbury, MA, 01545
Adv Exp Med Biol; 138:63-86 1982

Changes in uterine growth, morphology, and steroid receptor levels in female Syrian hamster pups injected with 100 ug diethylstilbestrol (DES: 40 mg/kg body wt) on the day of birth was investigated. Animals were either ovariectomized or sham-operated on day 3 of life, and some animals were given estrogen replacement (sc pellet estradiol). Alteration of uterine target cells occurred by direct action of DES during the neonatal period. Endometrial tumors were caused by chronic exposure of the DES-modified uterus to estrogen action later in life. (53 Refs)

16. HEPATOCARCINOGENICITY OF DIETHYLSTILBESTROL (DES) IN RATS (MEETING ABSTRACT).

Kamiya K, Seyama T, Kodama Y, Numoto M, Yokoro K
Department of Pathology, Hiroshima University, Hiroshima, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Despite the demonstration of carcinogenicity of DES in estrogen-susceptible tissues of some animal species, little is known about its carcinogenic effect in the liver. Castrated W/Fu rats treated with DES alone developed tumors of the liver (HT) in 30% of animals. By a combined treatment of DES and N-nitrosobutylurea (NBU) which is not hepatocarcinogen itself, HT incidence is much increased in several rat strains. In this system, androgen had no promotive effect in HT induction and the incidence correlated well with the dosage of DES. While castration prevents N-2-fluorenylacetamide (2-FAA) induced hepatocarcinogenesis, a combined treatment of 2-FAA and DES in castrated rats remarkably increased the incidence and tumor size of HT and shortened the latent period, suggesting the promotive effect of DES on the growth of transformed cells initiated by 2-FAA. Those results indicate that DES is a complete carcinogen with activities stronger in promotion than in initiation. (no Refs)

17. STRESS SEVERITY AND ADRENAL FUNCTION IN THE DEVELOPMENT OF THE DMBA-INDUCED RAT MAMMARY TUMOR: SOME PRELIMINARY INDICATIONS (MEETING ABSTRACT).

Newberry BH, Chambers LK, Boyle DA
Department of Psychology, Kent State University, Kent, OH, 44242
Psychobiologic, Psychophysiologic, Psychosomatic, and Psychosocial Aspects of Neoplastic Disease, 4th International Symposium, June 2-6, 1981, Bressanone, Italy European Working Grou p for Psychosomatic Cancer Research 25 pp., 1981.

One hypothesis which has appeared in several forms is that the function relating severity of presumably stressful stimulation (PSS) to animal tumor development is J-shaped, with mild PSS inhibiting, and severe PSS promoting tumor development. Our findings to date suggest that there can be genuine differences among mammary tumor systems in their responses to PSS; that increasing PSS severity does not change the response of the dimethylbenzanthracene (DMBA) induced rat mammary tumor (DMBA-RMt) from inhibition to enhancement; that severe, protracted adrenocortical activation need not indicate a particular tumor response to PSS; and that WBC levels are not strongly related to the response of the DMBA-RMt to PSS. Adrenal and thymus wt have regularly failed to suggest protracted adrenal corticoid responses to PSS which inhibits the DMBA-RMt. In mice, treatments which promoted and which failed to affect mammary tumors produced equal reductions in thymus/adrenal wt ratio. Diazepam, which suppresses the rise in corticosterone elicited by PSS, has produced at best a marginal blockage of the PSS effect on th DMBA-RMt in our experiments. Adrenalectomy promoted by the DMBA-RMT, but a second experiment - still in progress - suggests that adrenal demedullation may also promote this tumor. WBC counts were done in three recent experiments - the severe restraint, adrenalectomy, and diazepam experiments. In no case did leukocytopenia accompany aversive treatments. This again suggests the absence of long-term adrenocortical response to PSS which inhibits the DMBA-RMt. There was, in fact, some indication of higher WBC counts in animals exposed to PSS. This is consistent with, but does not require, an immunological explanation of the tumor's inhibition by PSS. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

18. EPIDEMIOLOGY OF CUTANEOUS MALIGNANT MELANOMA.

Balda BR
Dermatologische Klinik und Poliklinik der Universitat, Frauenlobstr. 9-11, D-8000 Munchen 2, W. Germany
MMW; 123(50):1923-1926 1981

Patterns of occurrence and possible causative factors in cutaneous malignant melanoma (MM) are reviewed. MM occurs in 1.8-28.57/100,000 persons, depending on the geographical area studied. A world-wide increase in incidence has been reported with rates increasing as much as 340% in 12 yr. MM occurs most frequently during middle age. Women are affected approx twice as often as men. Survival time after diagnosis is longer for women, however; this may be because MM of the trunk occurs most often in men. Approx 40% of MM carry estrogen receptors, suggesting that hormonal influences affect the incidence and progression of the disease. Avoidance of pregnancy and hormonal contraceptives is therefore recommended for women with MM. Approx 1-7% of MM are related to an autosomal dominant or polygenic factors. In precursor mole syndrom e atypical nevi become transformed into MM. A few cases of MM occurring in married couples have been reported that may be due either to infectious factors or to similarities in lifestyle. Ethnic and racial factors affect MM incidence; Celtic or Nordic types showing the highest incidence. Exposure to UV radiation has not been ruled out as a causative factor. Occurrence of MM in locations protected from sunlight suggests that a circulating factor is involved in tumor induction, but no such factor has been demonstrated. (65 Refs) (In GER)

19. LECTURE: THE INTERRELATION BETWEEN ENDOCRINOLOGY AND INTERNAL MEDICINE.

Kuang A
No affiliation given
Zhonghua Neike Zazhi; 20(4):237-241 1981

The roles of endocrine secretions in diseases and cancers are reviewed. Topics covered include the following: (1) endocrine secretions and pain, (2) endocrine secretions and fever (steroid fewer), (3) polypeptide hormones as tumor markers; (4) endocrine secretions in anemia and polycythemia, and (5) renal endocrine secretions and metabolic bone diseases. Ectopic hormones secretion is discussed, especially with reference for etiology and diagnosis of tumors. (no Refs) (In CHI)

20. NORMAL SISTER-CHROMATID EXCHANGES IN ORAL CONTRACEPTIVE USERS.

Husum B, Wulf HC, Niebuhr E
Dept. Anaesthesia, Rigshospitalet, Copenhagen, Denmark
Mutat Res; 103(2):161-164 1982

A group (A) of 63 women (15-42 yr old; av 22.3) who used no medication whatsoever was compared with a second group (B) of 52 women (16-43 yr old; av 26.3) who used oral contraceptives (OC; combinations of progestins and estrogens) with respect to the effect of cigarette smoking on sister chromatid exchanges (SCE) in peripheral lymphocytes. Mean numbers of SCE/cell ranged from 8.42-9.52 for group A, and 8.54-10.36 for group B, over a range of cigarette use of 0-greater than 20/day. The total number of SCE in 30 metaphases of each woman was transformed from an assumed Poisson distribution to a normal distribution, and a linear regression and Bartlett's test were performed which gave independent estimates of basic variance summed as 4.43 for group A and5.97 for group B. It was concluded that use of OC does not influence SCE in lymphocytes in either smoking or nonsmoking women. (8 Refs)

21. INHIBITION OF 7,12-DIMETHYLBENZ[A]ANTHRACENE- AND URETHAN-INDUCED LUNG TUMOR FORMATION IN A/J MICE BY LONG-TERM TREATMENT WITH DEHYDROEPIANDROSTERONE.

Schwartz AG, Tannen RH
Fels Res. Inst. and Dept. Microbiology, Temple Univ. Medical Sch., Philadelphia, PA, 19140
Carcinogenesis; 2(12):1335-1337 1981

Long-term treatment with the adrenal steroid dehydroepiandrosterone reduces weight gain without suppressing appetite and inhibits the occurrence of 7,12-dimethylbenz[a]anthracene- and urethan-induced lung tumors in A/J mice. (Author abstract) (26 Refs)

22. REGULATION OF PITUITARY GROWTH AND PROLACTIN GENE EXPRESSION BY ESTROGEN.

Lieberman ME, Maurer RA, Claude P, Wiklund J, Wertz N, Gorski J
Dept. Biochemistry and Animal Science, Univ. Wisconsin, Madison, WI, 53706
Adv Exp Med Biol; 138:151-163 1982

The site of estrogen action and the molecular events involved in the regulation of prolactin synthesis were studied using monolayer cultures of dispersed rat pituitary cells. Primary cultures of rat pituitary cells respond to estradiol by increased incorporation of precursors into prolactin. Time and magnitude of response are in agreement with that observed under in vivo conditions suggesting that estrogen exerts its effect through a direct action on the pituitary gland. Chronic treatment with diethylstilbestrol caused sustained proliferation of pituitary tumors in the Fisher 344 rat, but not in the Holtzman rat. (33 Refs)

23. REVERSAL OF THE PROMOTIONAL EFFECT OF 12-O-TETRA-DECANOYLPHORBOL-13-ACETATE ON MORPHOLOGICAL TRANSFORMATION OF HAMSTER EMBRYO CELLS BY GLUCOCORTICOIDS.

Rivedal E
Norwegian Radium Hosp., Montebello, Oslo 3, Norway
Cancer Lett; 15(2):105-113 1982

Effects of glucocorticoids and cholesterol on morphologic transformation by benzo(a)pyrene (BP) and 12-O-tetradecanoylphorbol-13-acetate (TPA) in hamster embryo cells were studied. Cells exposed to BP (0.05 ug/ml) during the first 3 days of incubation (period 1) and then to TPA (0.05 ug/ml) during the last 3 days (period 2) had a transformation frequency of 10.2%. When present during period 2, hydrocortisone and dexamethasone strongly inhibited the formation of transformed colonies. Corticosterone had only a slight inhibitory activity and cortisone had no inhibitory activity when administered in concentrations up to 25 uM. Dexamethasone, the most potent glucocorticoid, reduced transformation frequency by greater than 50% at 0.25 nanoM and completely abolished transformation at 250 nanoM. Cholesterol (2.5 or 25 uM) increased transformation frequency. The glucocorticoids had no effect when present only during period 1. The fact that addition of dexamethasone (250 nanoM) reduced transformation frequency even when added 6 hr before staining suggested that glucocorticoids rapidly reverse the morphology of transformed colonies back to normal. (31 Refs)

24. COMBINED EFFECTS OF 5-FLUOROURACIL (5FU) AND 2ALPHA DIMETHYLDEHYDROTESTOSTERONE PROPIONATE (2 ALPHA-MDTP) ON MCF-7 HUMAN BREAST CANCER CELLS IN CULTURE (MEETING ABSTRACT).

Fujita H, Teller MN, Stock CC
Division of Chemotherapy, Keio University School of Medicine, Tokyo, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

In vivo, the combination of 5-fluorouracil and 2 alpha dimethyldehydrotestostero ne propionate treatment showed at least an additive effect on dimethylbenzanthracene (DMBA)-induced rat mammary tumors. To examine the evaluation of combined effects of 5 FU and 2 alpha-MDTP on MCF-7 human breast cancer cells, measurements were made on the inhibitory effects on cell proliferation and of the incorporation of 14C-thymidine, 14C-uridine and 14C-leucine into cellular DNA, RNA and protein. Combination of 5 FU and 2 alpha MDTP in concentrations tested gave enhanced inhibition of cell proliferation and of the incorporation of the precursors into cellular macromolecular substances as compared with treatment by each agent. This enhanced effect is additive. (no Refs)

25. REDUCTION OF PROLINE TRANSPORT IN R3230AC MAMMARY CARCINOMAS BY ESTROGENS IN VITRO.

Hilf R, Helton DL
Dept. Biochemistry, Univ. Rochester Medical Center, 601 Elmwood Ave., Rochester, NY, 14642
Biochem Pharmacol; 31(1):37-41 1982

The effects of estrogens on proline and leucine transport into enzymatically dissociated cells from the R3230AC mammary adenocarcinoma were studied. Estradiol-17beta demonstrated a time- and dose-dependent reduction of proline transport; at 10(-6) M, transport of proline was decreased by 50%. Kinetic analysis of these effects indicate that estradiol displayed characteristics of a noncompetitive inhibitor, with a Ki of 1.79 uM. Other estrogens, and the anti-estrogen tamoxifen, gave somewhat higher estimated Ki values and could be ranked as inhibitors as follows: estradiol-17beta greater than diethylstilbestrol greater than tamoxifen greater than estriol approx = estrone greater than estradiol-17 alpha. No effects of these estrogens on leucine transport were observed, indicating their selectiveness for the A system. The synthetic glucocorticoid, dexamethasone, was comparable to diethylstilbestrol as an inhibitor of proline transport, but dexamethasone also decreased transport of leucine. Testosterone and progesterone were approximately comparable to estrone in their actions. It is proposed that these actions of estrogens represent one potential mechanism whereby pharmacological levels exert therapeutic benefit in the treatment of advanced breast cancer. (Author abstract) (23 Refs)

26. ENHANCED INHIBITION OF MAMMARY CARCINOGENESIS BY COMBINED TREATMENT WITH N-(4-HYDROXYPHENYL)RETINAMIDE AND OVARIECTOMY.

McCormick DL, Mehta RG, Thompson CA, Dinger N, Caldwell JA, Moon RC
Lab. Pathophysiology, Life Sciences Div., IIT Res. Inst., Chicgo, IL, 60616
Cancer Res; 42(2):508-512 1982

Bilateral ovariectomy and dietary administration of the retinoid N-(4-hydroxyphenyl)retinamide (4-HPR) are both effective inhibitors of chemical carcinogenesis in the rat mammary gland. The present study was designed to determine whether an enhanced inhibitory effect is obtained with combined ovariectomy and 4-HPR administration, compared to either treatment alone. In separate experiments, 50-day-old virgin female Sprague-Dawley rats received either a single iv injection of 50 mg N-methyl-N-nitrosourea per kg body wt or a single intragastric dose of 20 mg 7,12-dimethylbenz(a)anthracene. The experimental design was the same in both the N-methyl-N-nitrosourea and 7,12-dimethylbenz(a)anthracene experiments: Group 1, 25 intact rats, placebo diet; Group 2, 25 intact rats, supplement of 782 mg 4-HPR per kg diet; Group 3, 50 ovariectomized rats, placebo diet; Group 4, 50 ovariectomized rats, supplement of 782 mg 4-HPR per kg diet. Feeding of the 4-HPR supplement was begun 7 days after carcinogen administration; ovariectomy was performed 7 days post-7,12-dimethylbenz(a)anthracene or 14 days post-N-methyl-N-nitrosourea. In both experiments, combined ovariectomy plus 4-HPR was significantly more active in suppressing mammary cancer induction than was either manipulation alone. 4-HPR was a more effective inhibitor of carcinogenesis in ovariectomized rats than in intact animals. These data indicate that 4-HPR is highly effective in inhibiting ovarian hormone-independent cancers and suggest that retinoid inhibition of mammary carcinogenesis does not involve an influence on ovarian hormone action. (Author abstract) (19 Refs)

27. USE OF MULTIPLE TUMOUR MARKERS IN THE SCREENING FOR EARLY PRIMARY HEPATOCELLULAR CARCINOMA IN THE POPULATION IN SINGAPORE (MEETING ABSTRACT).

Oon CJ, Chio LF, Singh R, Chan L, Lim GK, Yo SL

Department of Medicine, National University of Singapore, Singapore General Hospital, Singapore 0316, Singapore

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

From 1979-1981 an ongoing prospective study was done on high-risk groups of the population in Singapore to determine the incidence of the primary hepatocellular carcinoma (PHC) in the various at risk groups. The groups studied were: 1000 normal males over 40 yr, 160 immediate PHC family members, 80 cirrhosis, 60 chronic hepatitis B carriers, 250 women on oral contraceptives and 50 males on androgen replacement therapy. Tumor markers used were Alphafetoprotein (AFP) (CIE), alpha1 antitrypsin (ATT), alpha1acidglycoprotein I, gammagglutamyl transpeptidase (GGT), and isocitrate dehydrogenase. Three of 1000 normal male population, (0.3%), 4/160 family PHC members (2.5%), 30/80 (38%) cirrhosis, 6/60 (10%) chronic hepatitis B carriers and 4/150 (1.6%) women on estrogen progesterone pills developed PHC. Hepatomegaly, (not due to a medical cause) was caused by PHC in 45/80 (56%) of patients. No male patients on normal androgen replacement therapy developed PHC after 3 yr follow up. AFP, ATT and GGT remain the most useful detector for PHC. Specific isoenzymes of ATT and GGT may be more useful in differentiating PHC from other conditions. Raised ATT levels in pill takers returned to normal on discontinuation. Only 10% of detectible tumors were resectible. All tumors detectible preclinically were 10 cm diameter (+/-) 2 cm. Three of 3 (100%) of these patients are alive at 1 yr follow up. (no Refs)

28. DETERMINATION OF A CONSTITUTIONAL PSYCHOSOMATIC FACTOR PROBABLY INFLUENCING TUMOR DEVELOPMENT IN MAN (MEETING ABSTRACT).

Audler AG
Schlossberg-Klinik, D8974 Oberstaufen, W. Germany
Psychobiologic, Psychophysiologic, Psychosomatic, and Psychosocial Aspects of Neoplastic Disease, 4th International Symposium, June 2-6, 1981, Bressanone, Italy European Working Group for Psychosomatic Cancer Research 25 pp., 1981.

Experiments in animals: Rabbits were injected with pilocarpine. Some of them recovered slowly from the intoxication, others more quickly. Two groups were formed on the basis of difference in recovery time. Both groups were injected with tumor mass. The slow-recovery group showed a significantly greater sensibility for the inoculation than the other group. Investigations in cancer patients: Two variables were compared in patients given surgical treatment for breast cancer, gastric cancer, sarcoma or melanoma. The survival time after operation was compared with the morning 11-hydroxycorticosteroid ('cortisol') level one yr before the closing date of the study or death. Values up to 31 mugr % cortisol in the serum were associated with a better prognosis in patients with breast and gastric carcinoma. No correlation was found in sarcoma and melanoma. We then compared the values obtained the first day after admission with the next value, determined about 7 days later. The first hospital admission can be expected to be a rather strong factor of stress for our patients. Cortisol levels decreasing after admission to 31 mugr % or less showed a better prognosis in breast and gastric carcinoma patients. Finally we compared the prognosis of all values above 31 mugr % with values fluctuating around 31 mugr %. The latter group showed a better prognosis. Proposals: (1) As slow recovery from stress is a risk factor for some cancers, this factor could be estimated. This can be done in many ways, even at an early age. (2) Treatment influencing the psyche-hypophysis-adrenal cortex-thymus axis might be developed as adjuvant therapy of some cancers, as well as a method of prophylaxis of tumor development in appropriate cases. (no Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Audier AG 28
Balda BR 18
Boyle DA 17
Brodie AM 13
Brodie HJ 13
Caldwell JA 26
Cappelletti V 11
Chambers LK 17
Chambless LE 2
Chan L 27
Chio LF 27
Claude P 22
Concolino G 8
Di Fronzo G 11
Dinger N 26
Djiane J 12
Evans RW 15
Fortmeyer HP 10
Fowler WC 2
Fujita H 24
Gilhar A 7
Gorski J 22
Greenberg BG 2
Haim S 7
Helton DL 25
Hendry WJ 15
Hilf R 25
Hulka BS 2
Husum B 20
Kamiya K 16
Kaufman DG 2
Kelly PA 12
Kodama Y 16
Kuang A 19
Leavitt WW 15
Levine L 14
Lieberman ME 22
Lim GK 27
Marocchi A 8
Maurer RA 22
Mauvais-Jarvis 5
McCormick DL 26
Mehta RG 26
Mehta RG 9
Michel RT 10
Moon RC 26
Moon RC 9
Newberry BH 17
Niebuhr E 20
Numoto M 16
Oon CJ 27
Petitti DB 1
Picardi C 8
Piva L 11
Pizzocaro G 11
Rivedal E 23
Romanoff L 13
Ronchi E 11
Ryan KJ 3
Schneider MR 10
Schonenberger H 10
Schwartz AG 21
Seyama T 16
Singh R 27
Sitruk-Ware R 6
Stock CC 24
Swan SH 1
Tannen RH 21
Teller MN 24
Thompson CA 26
Turcot-Lemay L 12
Veronese S 11
Vorherr H 4
Wertz N 22
Wiklund J 22
Williams JG 13
Williams KI 13
Wu JT 13
Wulf HC 20
Yo SL 27
Yokoro K 16

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.
Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

2. ETHYLENE DIBROMIDE (EDB). (REVISED).
NIOSH Document Development Branch
Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Curr Intell Bull NIOSH (37): 13 pp., 1981.

3. CHEMICAL CARCINOGENESIS AND SMOKING.
Farber E
Dept. Pathology, Univ. Toronto, Banting Inst., 100 College St., Toronto, Ontario M5G 1L5, Canada
Can J Public Health; 72(6):381-385 1981

RADIATION CARCINOGENESIS

4. CELLULAR TRANSFORMATION BY RADIATION: INDUCTION, PROMOTION, AND INHIBITION.
Borek C
Radiological Res. Lab., Cancer Center/Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 16(4):311-336 1981

5. EFFECTS OF IONIZING RADIATION ON THE DEVELOPING EMBRYO AND FETUS: A REVIEW.
Hoffman DA, Felten RP, Cyr WH
Bureau Radiological Health, Rockville, MD
Effects of Ionizing Radiation on the Developing Embryo and Fetus: A Review. Available from National Technical Information Service, Springfield, VA, as PB82-115379:, 160 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

6. BETA-CARBOLINES, PSYCHOACTIVE COMPOUNDS IN THE MAMMALIAN BODY.
Airaksinen MM, Kari I
Dept. Pharmacology, Univ. Kuopio, P.O. Box 138, SF-70101 Kuopio 10, Finland
Med Biol; 59(4):190-211 1981

7. DIET AND CANCER OF THE LARGE BOWEL.
Zaridze DG
Analytical Epidemiology Programme, Div. Epidemiology and Biostatistics, International Agency for Res. on Cancer, 150 Cours Albert Thomas, 69372 Lyon, Cedex 2, France
Nutr Cancer; 2(4):241-249 1981

8. INFLUENCE OF DIET ON MAMMARY CANCER.
Carroll KK
Dept. Biochemistry, Univ. Western Ontario, London, Ontario, N6A 5C1, Canada
Nutr Cancer; 2(4):232-236 1981

9. ARTIFICIAL SWEETENERS IN RELATION TO THE EPIDEMIOLOGY OF BLADDER CANCER.
Howe GR, Burch JD
NCI Canada Epidemiology Unit, Univ. Toronto, Ontario, Canada
Nutr Cancer; 2(4):213-216 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

10. EPIDEMIOLOGY AND THE STUDY OF CANCER.
Woods NF, Woods JS
Dept. Physiological Nursing, Sch. Nursing, Univ. Washington, Seattle, WA
Cancer Nursing. Marino LB, ed. St. Louis, The C. V. Mosby Company, 635 pp., 1981.

11. EPIDEMIOLOGY OF CUTANEOUS MALIGNANT MELANOMA.
Balda BR
Dermatologische Klinik und Poliklinik der Universitat, Frauenlobstr. 9-11, D-8000 Munchen 2, W. Germany
MMW; 123(50):1923-1926 1981
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12. THE SMOKING-INDUCED EPIDEMIC.
Doll R
Green Coll. Oxford, Oxford, England
Can J Public Health; 72(6):372-381 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

13. HEALTH HAZARDS OF ASBESTOS EXPOSURE.
Kaw JL
Industrial Toxicology Res. Centre, Lucknow 226 001, India
J Sci Ind Res; 40(5):342-346 1981

14. OVERVIEW OF FINNISH EPIDEMIOLOGIC STUDIES ON OCCUPATIONAL CANCER.
Tola S
Dept. Epidemiology and Biometry, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(Suppl4):133-139 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

15. ALKYLATION OF DNA AND TISSUE SPECIFICITY IN NITROSAMINE CARCINOGENESIS.
Montesano R
International Agency for Res. on Cancer, 150, Cours Albert Thomas, 69372 Lyon Cedex 2, France
J Supramol Struct Cell Biochem; 17(3):259-273 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

16. TRANSFORMATION INDUCED BY HERPES SIMPLEX VIRUS: A POTENTIALLY NOVEL TYPE OF VIRUS-CELL INTERACTION.
Hampar B
Lab. Molecular Virology, NCI, Frederick, MD, 21701
Adv Cancer Res; 35:27-47 1981

17. ONCOGENESIS BY RNA TUMOR VIRUSES.
Koyama T
Dept. Carcinostasis Res., Tokyo Univ. Medical Res. Inst., 4-6-1 Kindai, Minato-ku, Tokyo 108, Japan
Tanpakushitsu Kakusan Koso; 26(14):2121-2129 1981
In JPN

18. POLYOMA T ANTIGENS.
Eckhart W
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
Adv Cancer Res; 35:1-25 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

19. EPIDEMIOLOGICAL ASSESSMENT OF DIETARY INTAKE.
James WP, Bingham SA, Cole TJ
Medical Res. Council's Dunn Clinical Nutrition Center, Adenbrooke's Hosp., Cambridge, England
Nutr Cancer; 2(4):203-212 1981

20. ASSESSMENT OF TECHNOLOGIES FOR DETERMINING CANCER RISKS FROM THE ENVIRONMENT.
Office of Technology Assessment
Office of Technology Assessment, Washington, DC
Assessment of Technologies for Determining Cancer Risks from the Environment. Available from National Technical Information Service, Springfield, VA, as PB81-235400:, 243 pp., 1981.

21. ANTIBODIES SPECIFIC FOR DNA COMPONENTS STRUCTURALLY MODIFIED BY CHEMICAL CARCINOGENS.
Muller R, Rajewsky MF
(c/o Rajewsky) Institut fur Zellbiologie (Tumorforschung), Universitat Essen (GH), Hufelandstrasse 55, Essen 1, W. Germany
J Cancer Res Clin Oncol; 102(2):99-113 1981

22. APPLICATION OF THE MICROBIAL MUTATION TEST IN OCCUPATIONAL HEALTH AND ITS FUTURE PROBLEMS.
Takemura N
Dept. Public Health, Jikei Univ., 25-8, Nishi-Shimbashi 2-chome, Minato-ku, Tokyo, 105, Japan
Sangyo Igaku; 23(4):355-365 1981
In JPN

OTHER REVIEWS IN CARCINOGENESIS

23. ARACHIDONIC ACID TRANSFORMATION AND TUMOR PRODUCTION.
Levine L
Dept. Biochemistry, Brandeis Univ., Waltham, MA, 02254
Adv Cancer Res; 35:49-79 1981

24. POLYAMINES IN MAMMALIAN TUMORS PART 1.
Scalabrino G, Ferioli ME
Inst. General Pathology, Univ. Milan, 20133 Milan, Italy
Adv Cancer Res; 35:151-268 1981

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In this issue:

- **ORAL CONTRACEPTIVES AND HUMAN CANCER** 1-2
- **ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER** 3-7
- **MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES** 8-13
- **MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES** 14-16
- **HORMONAL CARCINOGENESIS IN ANIMALS** 17-22
- **REVIEWS AND OTHER RELATED STUDIES** 23-42

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

ORAL CONTRACEPTIVES AND HUMAN CANCER

1. EPIDEMIOLOGICAL STUDIES OF THE ROLE OF EXOGENOUS ESTROGENS IN THE ETIOLOGY OF BREAST CANCER.

Kelsey JL, Bulbrook RD, Korenman SG, Siiteri PK, Henderson BE
Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Banbury Rep; 8:215-228 1981

Epidemiological studies of the relationship between use of oral contraceptives (OC) and estrogen replacement therapy to the development of breast cancer are reviewed. No major study of OC has demonstrated a positive or negative overall association. With at least a 15-yr latent period, current studies will better evaluate the association between OC and breast cancer. Studies on estrogen replacement have p rovided conflicting results; no firm conclusion has been made. (48 Refs)

2. STRUCTURAL FORMS OF CARCINOGENESIS IN THE PORTIO-CERVIX REGION UNDER THE INFLUENCE OF EXOGENOUS HORMONES.

Dallenberg-Hellweg G
Frauenklinik im Klinikum Mannheim, Universitat Heidelberg, Morphologische Abteilung, D-6800 Mannheim 1, W. Germany
Pathologe; 3(1):13-24 1981

A possible relationship between the use of exogenous hormones (eg, oral contraceptives or gestagen therapy) and the development of cancerous and precancerous lesions in the uterine cervix is discussed. The effects of estrogens and gestagens on the epithelium of the portio and cervical mucosa are described, and early stages of epithelial hyperplasia are detailed. Malignant development of regeneration epithelium of the portio and reserve epithelium of the cervix is outlined, with emphasis on the effects of exogenous hormones. Histological characteristics are detailed for the following precancerous and cancerous lesions: dysplasia, carcinoma in situ, microcarcinoma, invasive squamous cell carcinoma, mucoepidermoid carcinoma, clear cell carcinoma, and adenocarcinoma. The development of the latter type of malignancy from atypical adenomatous hyperplasia and adenocarcinoma in situ is examined in detail; the effects of hormones are considered. It is concluded that, while no direct relationship between hormone administration and development of squamous cell carcinoma has been established, there is substantial evidence of such a relationship between hormone administration and the development of adenocarcinoma of the cervical mucosa. (26 Refs) (In GER)

ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER

3. ESTROGENS AND PROGESTERONE IN HUMAN BREAST CANCER.

Cole P
Epidemiology Program, Univ. Alabama in Birmingham, Comprehensive Cancer Center, Birmingham, AL, 35294
Banbury Rep; 8:109-113 1981

The role of endogenous estrogens in induction of human breast cancer is discussed. The following questions were addressed. Is the total amount of estrogens and their balance important? Do other hormones modify the carcinogenic effects of estrogens? Is an external or environmental factor involved? Are the carcinogenic effects of estrogens maximal during a segment or phase of the menstrual cycle of woman's life? (14 Refs)

4. PROLACTIN - AN IMPORTANT HORMONE IN BREAST NEOPLASIA?

Henderson BE, Pike MC, Moon RC, Segaloff A, Bulbrook RD, Meites J, Siiteri PK, Shellbarger CJ, Cole P
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep; 8:115-130 1981

The role of prolactin in the development and growth of breast tumors is discussed. After the first full-term pregnancy, a woman's plasma prolactin level may be permanently lowered, perhaps providing protection against the development of breast cancer. Breast cancer patients and their high-risk family members generally have elevated prolactin levels. Prolactin level has not been correlated with wt or any dietary nutrients. Prolactin may enhance the mitogenic effect of estrogen. (30 Refs)

5. HORMONE PROFILES IN YOUNG WOMEN AT RISK OF BREAST CANCER: A STUDY OF OVARIAN FUNCTION DURING THEELARCHE, MENARCHE, AND MENOPAUSE AND AFTER CHILDBIRTH.

Brown JB, Siiteri, Pike MC, Henderson BE
Dept. Obstetrics and Gynecology, Univ. Melbourne, Parkville, Victoria, 3052, Australia
Banbury Rep; 8:33-56 1981

Ovarian functions of women at various stages of their reproductive life were studied to find out more about the role of hormonal changes as a risk factor in breast cancer. Results of the study of the normal ovulatory cycle, anovulatory cycles, absent ovarian activity, values found in children, longitudinal studies over menarche, returning fertility after childbirth, and waning ovarian activity at the menopause are presented It was indicated that during normal ovulatory cycle, increased estrogen values in the absence of raised progesterone values occur for an av of 5 days only. Two types of anovulatory cycles can be identified: no human yet has been encountered who does not excrete estrogens in the urine as measured by methods of sufficiently high sensitivity, and anovulatory cycles that are much more common in teenage girls, after childbirth, and during the approach to menopause. (7 Refs)

6. BREAST CANCER: DIET AND HORMONE METABOLISM.

Hill P, Garbaczewski L, Kasumi F, Kuno K, Helman P, Wynder EL, Topp W, Pike MC, Henderson BE, Segaloff A, Sirbasku DA, Korenman SG, Cole P, Zumoff B
Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Banbury Rep; 8:257-277 1981

The effect of diet modification on hormonal metabolism of women at low risk (black South African and Japanese) and women at high risk (North American caucasian) for breast cancer was investigated. Differences in the hormonal profile during the menstrual cycle between the three races of women were noted. Differences in pituitary response in circulating hormone levels and in duration of menstrual cycle occurred when a Western diet was interchanged for a vegetarian diet, and vice versa. The therapeutic value of this observation is unknown. (94 Refs)

7. EPIDEMIOLOGY OF HEPATIC ANGIOSARCOMA IN THE UNITED STATES: 1964-1974.

Falk H, Herbert J, Crowley S, Ishak KG, Thomas LB, Popper H, Caldwell GG
Chronic Diseases Div., Center Environmental Health, Centers Disease, Control, Public Health Service U. S. Dept. Health and Human Services, Atlanta, GA, 30333
Environ Health Perspect; 41:107-113 1981

The occurrence of hepatic angiosarcoma (HAS) in the United States was studied fo r the period 1964-1974. Death certificates were reviewed in 22,432 cases of death due to liver tumors. Based on examination of medical records and pathological specimens, 168 cases of HAS were confirmed. Of cases identified as HAS on death certificates, only 42% were confirmed as HAS by other evidence; 50% were confirmed as not HAS. Only 23% of confirmed cases of HAS would have been identified by a search of death certificates alone. Inadequacies in epidemiolgical studies are indicated. HAS occurred predominantly in men (male:female ratio 3:1) and more frequently in the younger age groups. The mean age was 50.1 yr for women and 57.9 yr for men. Of 127 men with HAS, 12 had been exposed to vinyl chloride (VC), 15 to Thorotrast (TT), 4 to inorganic arsenic (As), and 3 to androgenic-anabolic steroids (AAS); 93 cases were classified as idiopathic. Of 41 women with HAS, 5 had been exposed to TT, 2 to As, and 1 to AAS; 33 cases were classified as idiopathic. A relationship between HAS and VC, TT, or AAS was more common in the latter part of the study period, probably due to recent introduction of VC and AAS and a long latency period for TT. The mortality rate for HAS was 0.75 cases/10(7) population/yr. The mortality rate was apparently higher in industrialized areas of the Northeast and Midwest and lower in farming states and the South; differences in rates for different areas may have been due to reporting methods rather than to actual differences in occurrence. Four agents have been identified as probable causative factors in HAS, but 75% of cases are of uncertain etiology. (28 Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES

8. SEX-STEROID RECEPTORS IN MALIGNANT TUMORS.

Saez S
Centre Leon Berard, 28, rue Laennec, F 68373 Lyon Cedex 2, France
Ann Endocrinol (Paris); 42(4/5):306-314 1981

Relationships among steroid receptors and carcinogenesis, tumor growth, and cancer therapy are reviewed. Steroids favor the development of cancer through the stimulation of the growth of epithelium particularly in the breast, endometrium, and prostate gland. Disequilibration of hormones and hormone receptors metabolism appears to be related to carcinogenesis. Estrogen and progesterone receptors are discussed in relation to breast cancer. The development of vaginal cancer from ectopic epithelial cells following diethylstilbestrol exposure is described. Appearance of androgen and estrogen receptors in the colon following treatment with carcinogenic agents indicates that carcinogens themselves are related to the appearance and increase of hormone receptors. The clinical significance and the therapeutic implications of the presence of hormone receptors in breast, endometrium, and prostate is discussed. The exact content of receptors in a tumor is determined in part by the structure of the tissue and number of epithelial cells present. Cancer development seems to depend on the levels of receptors. The presence of hormone receptors in other cancers is considered. (28 Refs) (In FRE)

9. STEROID RECEPTORS AS PROGNOSTIC INDICATORS IN PATIENTS WITH MAMMARY CANCER.

Bulic N, Budisic Z, Naranck P, Stojkovic R, Kubovic M, Gamulin S, Kosovel E, Martinac P, Montani Dj, Unusic J
Zavod za klinicku onkologiju i radioterapiju, Medicinski fakultet Sveucilista u Zagrebu, Zagreb, Yugoslavia
Libri Oncol; 10(2/3):317-321 1981

Estrogen receptors (ER) and progesterone receptors (PgR) were determined in 205 patients with mammary carcinoma. Twenty one percent of the patients were in Stage I, 61% in Stage II, and 18% in Stage III. Possible response to therapy was rated R for the patients with tumors containing ER greater than 100 femtomoles (fmol)/mg protein (pr) or ER greater than 3 fmol/mgpr and with PgR greater than 20 fmol/mgpr, R for the patients with ER between 3-100 fmol/mgpr, and PgR- or ER- and PgR greater than 20 fmol/mgpr, and R- for the remaining patients. The 113 patients in Stage I and in Stage II were evaluated for 18 mo after surgery; of the 36 patients rated R none had relapse; of the 20 patients rated R, 8/20 had relapse, and three of them died; and of 57 rated R-, 12/57 had relapse, and 5 of them died. The 94 patients in Stage I and Stage II were evaluated for 24 mo after surgery; of the 25 patients rated R, 2 had relapse, and 1 of them died; of the 19 patients rated R, 9 had relapse, and 3 of them died; and of the 50 patients rated R-, 17 had relapse, and 9 of them died. Discrepancy in results between R and R- could be due to adjuvant chemotherapy administered in higher percentage to the patients rated R-. Patients with low or negative values of the steroid receptors should be considered at high risk. (11 Refs) (In SCR)

10. CHANGES IN ESTROGEN RECEPTOR LEVELS DURING DES-INDUCED HEPATOCARCINOGENESIS IN THE SYRIAN HAMSTER FED ALPHA-NAPHTHOFLAVONE.

Li SA, Li JJ
Medical Res. Lab., Veterans Admin. Medical Center, Minneapolis, MN, 55417
J Steroid Biochem; 15:387-392 1981

Incidence of hepatocarcinogenesis was investigated in diethylstilbestrol (DES)-treated castrated and ovariectomized Syrian golden hamsters fed 0.2% alpha-naphthoflavone (ANF) in the diet. Induction of liver tumors (LT) by DES was essentially nil. When similar DES-treated castrated male hamsters were maintained on a diet containing ANF, nearly 70% developed LT. No LT were found in hamsters treated with ANF alone. Diet containing beta-naphthoflavone alone, or in the presence of DES did not induce LT. Competition with 250-fold excess nonlabeled DES for tritiated estradiol (ED) binding indicated that only the 8S moiety of estrogen receptors (ER) was specific. The specificity of ER in cytosol was indicated by minimal inhibition when either radioinert cortisol, progesterone, methyltrienolone, or triamcinolone acetonide was used at the same concentration. The binding of [3H]-ED in DES plus ANF-treated liver cytosol was saturable and of high affinity with an association constant of 0.15-1.3 x 10(9) M-1. Similar results were obtained using liver cytosol derived from untreated castrated and DES-treated hamsters. DES treatment for 3-4 mo resulted in a 2.5-fold increase in specific estrogen binding, and treatment with DES plus ANF for a similar period induced a 3.5-5-fold increase in liver ER concentration. In both treated groups when sedimented in high salt sucrose gradients, 4S nuclear binders were detected for liver ER. Cytosol-nuclear receptor translocations carried out either in the presence of nonlabeled DES or at 0-3 C exhibited little nuclear uptake of the labeled ED in all tissues examined. (37 Refs)

11. SPONTANEOUS CANINE MAMMARY TUMORS: A MODEL FOR HUMAN ENDOCRINE THERAPY?

Raynaud JP, Cotard M, Andre F, Mialot JP, Rolland PH, Martin PM
Roussel-Uclaf, 75007 Paris, France
J Steroid Biochem; 15:201-207 1981

The possibility of presence of estrogen (ER) and progestin receptors (PR) as markers for hormone-dependence in canine and in human mammary tumors (MT) was studied in an analysis of MT from 144 pet bitches. MT were analyzed for steroid hormone receptor (SHR) content and were submitted to pathological examination. No significant difference was noted in the prevalence of MT among different breeds, and SHR incidence did not vary significantly. SHR content was not related to age and its presence was similar in virgins and dams. The mean age of bitches with ER- and PR-positive tumors was 9.96 yr compared to 10.43 yr for the ER- and PR-negative group. Progestin treatment for contraceptive purposes had no significant effect on the incidence of SHR in MT. SHR were present more frequently in multinodular, than in single MT, and only 33% of all single MT had both ER and PR. MT were classified into three categories according to size of the tumor, but the incidence of SHR did not vary significantly among the groups. Incidence of ER and PR was quite similar in benign and malignant MT, but when present, the concentrations of either ER or PR tended to be higher in benign, than in malignant tumors. Benign epithelial and mixed tumors had similar incidence of ER and PR, approx 56%, while of all malignant MT 53% contained ER, 52% PR, and 44% both ER and PR. Results indicate that the canine MT could be an appropriate model for human breast cancer. (31 Refs)

12. THREE RADIOLIGANDS COMPARED FOR DETERMINING CYTOPLASMIC ESTROGEN-RECEPTOR CONTENT OF HUMAN BREAST CARCINOMAS.

Pieslor PC, Gibson RE, Eckelman WC, Oates KK, Cook B, Reba RC
(c/o Eckelman) Radiopharmaceutical Chemistry, George Washington Univ. Medical Center, 2300 I St. NW, Washington, DC, 20037
Clin Chem; 28(3):532-537 1982

We compared three radioligands for use in a cytoplasmic estrogen-receptor assay, using pooled cytosol from human breast adenocarcinomas. The estrogen receptor content was determined in vitro by a dextran-coated charcoal method involving a 4-hr incubation with and without diethylstilbestrol. Tritiated moxestrol failed to come to equilibrium in 4 hr, thereby preventing the use of conventional one-component Scatchard analysis. The use of 125I-labeled estradiol resulted in a higher estimate of estrogen-receptor concentration than that obtained with use of tritiated estradiol. This overestimation was not corrected by Scatchard, double-reciprocal, or Woolf plots, or by two different methods of data analysis: least squares and 'robust.' An underestimation of the specific activity of iodoestradiol with respect to that of tritiated estradiol and an unrecognized second component of nonreceptor binding could explain this disparity. (Author abstract) (24 Refs)

13. ESTROGEN REGULATION OF RAT PROSTATE ANDROGEN RECEPTOR.

Bouton MM, Pornin C, Grandadam JA
Centre de Recherches Roussel-UCLAF, 93230 Romainville, France
J Steroid Biochem; 15:403-408 1981

Estrogen regulation of rat prostate androgen receptor (AR) was studied. Results for effects of estrogen on cytosol AR and of anti-estrogen treatment on the estrogen-induced increase in cytosol AR, and cytosolic estrogen receptor (ER) in rat prostate are presented. Estrogens which do not interact with AR (moxestrol, diethylstilbestrol, ethynyl estradiol) are also able to increase cytosolic AR and the increase might be mediated by the ER present. (36 Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES

14. OXIDATIVE METABOLISM OF DIETHYLSTILBESTROL BY PROSTAGLANDIN SYNTHETASE.

Degen GH, Eling TE, McLachlan JA
(c/o McLachlan) Transplacental Toxicology Section,, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Cancer Res; 42(3):919-923 1982

The cooxidative metabolism of the transplacental carcinogen, diethylstilbestrol (DES), was examined using ram seminal vesicle microsomes. The major extractable metabolite was beta-dienestrol (Z,Z-DIES) and represented about 35% of the added DES in 3-min incubations supplemented with arachidonic acid. Its formation was dependent upon the presence of arachidonic acid, whereas reduced nicotinamide adenine dinucleotide phosphate failed to elicit Z,Z-DIES above background. Indomethacin and 1-phenyl-3-pyrazolidone, known inhibitors of prostaglandin synthetase, blocked Z,Z-DIES formation, probably by inhibiting the cyclooxygenase and the hydroperoxidase activities, respectively. Hydrogen peroxide and 15-hydroperoxyarachidonic acid (cosubstrates of the prostaglandin synthetase-hydroperoxidase), when replacing arachidonic acid in incubations, also supported oxidative metabolism of DES catalyzed by ram seminal vesicle microsomes. 1-Phenyl-3-pyrazolidone, but not indomethacin, inhibited the 15-hydroxyperoxy arachidonic acid-dependent formation of Z,Z-DIES. Incubation conditions which supported efficient Z,Z-DIES formation also resulted in the formation of 3,3-di(p-hydroxyphenyl)hexan-4-one and the cis-isomer of DES as well as nonextractable, protein-associated radioactivity indicating the presence of reactive intermediates. The implications of the peroxidative metabolism of DES for its toxic activity are obvious. (Author abstract) (40 Refs)

15. REGULATION OF GAMMA-GLUTAMYLTRANSPEPTIDASE IN RAT HEPATOCYTE MONOLAYER CULTURES.

Edwards AM
Clinical Biochemistry, Sch. Medicine, Flinders Univ. South Australia, Bedford Park, South Australia 5042, Australia
Cancer Res; 42(3):1107-1115 1982

Hepatocytes isolated as a relatively pure population from normal adult rats were maintained in primary monolayer culture for 4 to 7 days on plastic dishes. Factors affecting activity of gamma-glutamyltranspeptidase (GGT) in culture were investigated to establish a basis for in vitro studies on carcinogen-induced changes in GGT. Freshly plated cultures contained few GGT-positve cells (0.4%) and very low total GGT activity, but with all media tested, activity increased progressively with time in culture, the extent of increase depending on medium composition. For hepatocytes in modified Waymouth medium alone (control cultures), there was a slow rise in activity after a 1-to 2-day lag period. This increase was enhanced up to 10-fold in the presence of 3 uM dexamethasone for cells on plastic but only 2-to 3-fold for cells on collagen gels. The time- and dose-dependent action of dexamethasone was prevented by cycloheximide, partly blocked by actinomycin D, and reversed after several hr by removing the steroid, when GGT activity decreased with a max half-life of 60 to 80 hr. These observations suggest that dexamethasone caused reversible enzyme induction dependent on continuing RNA and protein synthesis. Cell maintenance with fetal calf serum or with N6,mO21-dibutyryl adenosine 3':5'-monophosphate or glucagon markedly reduced the extent of induction by dexamethasone and slightly lowered activity in control cultures. Maintenance at lower pH within the range of 7.2 to 7.8 or at higher glucose concentrations within the range of 2.8 to 28 mM also resulted in markedly lower GGT activities in control or dexamethasone-induced cultures. Glucose repression was independent of insulin concentration. The reversible induction and repression of GGT may reflect broad changes in hepatocyte gene expression rather than specific controls of GGT function. Since GGT in cultured hepatocytes is subjected to regulation by a variety of noncarcinogens, caution is required in its use as a preneoplastic marker. Nevertheless, the identification of culture media which preserve low activity may allow studies on carcinogen-induced changes in GGT as a probe of the early events in vitro hepatocarcinogenesis. (Author abstract) (62 Refs)

16. EFFECTS OF ESTROGENS ON ARYL HYDROCARBON HYDROXYLASE MEDIATED BINDING OF BENZO(A)PYRENE METABOLITES TO DNA IN VITRO.

Williams MT, Hendley R
Dept. Biochemistry, Coll. Medicine, Univ. South Florida, Tampa, FL, 33612
Biochem Biophys Res Commun; 104(4):1349-1355 1982

Liver microsomes from mice injected with 0.1 or 2 mg of estradiol (ES) 24 prior to, during and 24 hr after injection of 3-methylcholanthrene (MC), exhibited a significantly decreased capacity to mediate the binding of benzo(a)pyrene metabolites to DNA, compared to microsomes from mice which received only MC. The enzyme and cytochrome components of the aryl hydrocarbon hydroxylase (AHH) were not affected by either ES treatment, suggesting ES may act as a non-competitive inhibitor of AHH activity. (20 Refs)

HORMONAL CARCINOGENESIS IN ANIMALS

17. THE ROLE OF OVARIAN STEROID HORMONES IN MAMMARY CARCINOGENESIS.

Dao TL, Henderson BE, Welsch CW, Moon, Cole, Segaloff, Sirbascu, Zumoff BJ
Dept. Breast Surgery and Breast Cancer Res. Unit, Roswell Park Memorial Inst., Buffalo, NY, 14263
Banbury Rep; 8:281-298 1981

The role of ovarian steroid hormones on the pathogenesis of mammary cancer both in vivo and in vitro is described. Induction of mammary cancer by ovarian hormones were studied, and the following experiments were performed: castration related to induction of mammary carcinogenesis in rats (female and male), and induction of mammary tumors by local application of the carcinogen. Studies on relationship between prolactin and estrogen in mammary tumor growth and in vitro studies of mammary carcinogenesis are presented. (19 Refs)

18. PROLACTIN AND GROWTH HORMONE IN THE DEVELOPMENT, PROGRESSION, AND GROWTH OF MURINE MAMMARY TUMORS.

Welsch CW
Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:299-315 1981

The role of prolactin and growth hormone in the development and growth of spontaneous rodent mammary tumors, were examined. Growth of transplantable rodent mammary tumors, and development and growth of carcinogen-induced rat mammary tumors were also examined. Prolactin is important in initiating and promoting phases of murine mammary tumorigenesis, while the role of growth hormone appears to be less important. The role of growth hormone in the oncogenesis remains to be determined. (72 Refs)

19. PITUITARY AND STEROID HORMONES IN RADIATION-INDUCED MAMMARY TUMORS.

Shellabarger CJ
Medical Dept., Brookhaven National Lab., Upton, NY, 11973
Banbury Rep; 8:339-351 1981

Advantages of the radiation-induced (RI) rat mammary tumor system as a mode for studying RI breast cancer in humans and the rat mammary fibroadenoma response to irradiation are discussed. Evidence for chemically induced carcinogenesis and RI carcinogenesis is compared. Estrogen synergism in mammary carcinogenesis is reviewed; women whose cancer is 'initiated' women may develop breast cancer if the disease is 'promoted,' even if the promotion occurs years after initiation. (57 Refs)

20. INFLUENCE OF PREGNANCY AND LACTATION ON EXPERIMENTAL MAMMARY CARCINOGENESIS.

Moon RC, Shellabarger CJ, Henderson BE, Pike MC, Dao TL, Meites J, Sinha YN
Life Sciences Div., IIT Res. Inst., Chicago, IL, 60616
Banbury Rep; 8:353-364 1981

The influence of pregnancy and lactation on experimental mammary carcinogenesis (MC) was studied in Sprague-Dawley female rats; 7,12-dimethylbenz(a)anthracene (DMBA)-induced MC in the rat is influenced by parity. The effect of age at which the first litter is borne on DMBA-induced MC, when MC is initiated at a subsequent period in the life of the animal, was examined. The age at which pregnancy ensues did not appear critical in the rat. Tumor hormone responsiveness in primiparous rats appears related to the age at which pregnancy occurs; pregnancy may alter the sensitivity of mammary cells to stimulatory hormones. (19 Refs)

21. PERMISSIVE ROLE OF THE PITUITARY IN THE INDUCTION AND GROWTH OF ESTROGEN-DEPENDENT RENAL TUMORS.

Lin YC, Loring JM, Villee CA
(c/o Villee), Harvard Medical Sch., Boston, MA, 02115
Cancer Res; 42(3):1015-1019 1982

Prolonged administration of estrogen to hamsters by implanted pellets induces not only renal adenocarcinomas but also enlarges pituitaries with hyperplastic and neoplastic changes, especially in the pars intermedia. The pituitaries of the diethylstilbestrol-implanted animals weigh 90 to 150 mg; those of control animals without diethylstilbestrol pellets weigh 7 to 12 mg. Castrated male hamsters were hypophysectomized, implanted with diethylstilbestrol pellets, fed laboratory chow ad libitum, and given 5% glucose in water to drink. New pellets were implanted every 3 mo, and the animals survived for 12 to 15 mo. At autopsy, none of the animals had a tumor. Sixty-two of 65 control castrated males with the same schedule of pellet implantation developed tumors. Hypophysectomized castrated males implanted with diethylstilbestrol pellets were given daily injections of 1 ug each of follicle-stimulating hormone, luteinizing hormone, and prolactin; or with 0.9% NaCl solution. These animals survived for 12 to 15 mo, but none developed kidney tumors. Other castrated males were hypophysectomized and implanted with diethylstilbestrol pellets, and 2 mo later tumor tissues were transplanted under the kidney capsule. Eighty days later, no tumors were evident in the kidneys of these animals. Control castrated males were implanted with diethylstilbestrol pellets, and 2 mo later tumor tissue was transplanted under the kidney capsule. Between 60 and 85 days later, 13 of the 15 controls had developed renal tumors. The concentrations of circulating follicle-stimulating hormone and luteinizing hormone in animals with diethylstilbestrol implants decreased with time and, by 7 mo, were similar to those in hypophysectomized animals. The concentration of prolactin in animals with diethylstilbestrol pellets increased with time and reached twice the value in the control animals without diethylstilbestrol pellets. These studies suggest that some factor secreted by the pituitary may be involved as a promoter or a cocarcinogen in the estrogen induction of kidney tumors. (Author abstract) (19 Refs)

22. EFFECTS OF NORETHYNODREL ON NEOPLASMS IN THE BUCCAL POUCH OF THE SYRIAN HAMSTER.

Frenslli JA, Weathcrred JG
416 Hungerford Dr., Rockville, MD, 20850
Oral Surg; 53(3):288-292 1982

This study was instituted to determine the effect of a progestin, norethynodrel, on the induction of experimental carcinomas of the hamster cheek pouch. Thirty-six Syrian hamsters were divided into two groups. One group received 2 mg/kg/day of norethynodrel in sc injections, and the other group received nothing. The right cheek pouches of both groups were painted 3x a wk with the chemical carcinogen 9,10-dimethyl-1,2-benzanthracene in a 0.05% acetone solution. After 9 wk of painting, the first tumors developed in the hormone-treated hamsters, while none appeared in the control group until after 10 wk. After 15 wk, 100% of both groups had tumors. The average latent period was 11.8 wk for the treated group and 12.7 wk for the control group, (p = less than 0.05%, Student's test). Norethynodrel significantly decreased the induction time of the neoplasms. (Author abstract) (12 Refs)

REVIEWS AND OTHER RELATED STUDIES

23. ROLE OF HORMONES IN MAMMOGENESIS AND CARCINOGENESIS.

Nandi S, Yang J, Richards J, Guzman R, Shellabarger CJ, Rosen JM, Sirbasku DA, Siiteri PK, Korenman SG
Dept. Zoology and Cancer Res. Lab., Univ. California, Berkeley, CA, 94720
Banbury Rep; 8:445-456 1981

Development of a collagen system for growing mammary cells in vitro is described. Results for general aspects of growth of mammary cells inside collagen gel matrix (CGM), growth of normal mouse mammary epithelial cells (MEC) inside CGM (effects of hormones and growth factors), and for growth of normal human MEC inside CGM (effects of hormones and tissue extracts) are presented. Explanation for the observation that mammogenic hormones are growth-promoting in vivo appears to be in the fact that hormone-induced growth of a tissue or organ in vivo is a complicated phenomenon encompassing a number of biological events at the tissue level, including cell division; hormones might be the ultimate regulators of tissue growth, although they are not directly mitogenic. (27 Refs)

24. ORAL CONTRACEPTIVES: VOLUME 5.

Briggs MH, Briggs M
Deakin Univ., Geelong 3217, Australia
Oral Contraceptives: Volume 5. St. Albans, VT, Eden Medical Research Inc., Annual Research Reviews–Endocrinology, 331 pp., 1981.

Clinical trials, side effects, pharmacology, biochemistry, metabolism, and sociology of oral contraceptives (OC) are reviewed and discussed. Alternatives to the pill, new OC (combined oral products, OC for men), and older OC and therapeutic uses of contraceptive steroids are discussed, including their use in cancer therapy. Mortality and cardiovascular disease, hypertension, thrombosis, amenorrhea, and liver are affected by OC. Malformations and effect on offspring caused by diethylstilbestrol and other contraceptive steroids are reviewed. The role of OC in the genesis of breast, uterine endometrium, cervix, liver, and other neoplasms is discussed. OC may cause neurological, psychological, and other effects. Immunity and infection may be affected by OC. Mode of action, toxicology, contraceptive steroid metabolism, drug interactions, pharmacy, pharmacokinetics, and pharmacodynamics of OC are presented. Biochemistry and metabolism of OC are reviewed focusing on endocrinology (sex hormones, corticosteroids, protein hormones) and vitamins. (1179 Refs)

25. VASCULAR LEIOMYOMA.

Tsoutsouris GV
7127 Indianapolis Blvd., Hammond, IN, 46324
J Foot Surg; 21(1):37-41 1982

Clinical appearance, etiology, histopathology, treatment, and prognosis of vascular leiomyoma (VL) are reviewed. VL often simulates ganglionic cysts, lipomas, fibromas, and glomus tumors. Definite diagnosis depends on histologic appearance. Etiologic factors include trauma, infections, hormones, familial and hereditary factors, and possibly induction of mesenchymal cells of loose connective tissue to form smooth muscle. The case of a 34-yr-old man with a painful mass overlying the middle cuneiform of the left foot of several mo duration is presented. The mass was excised and the patient was asymptomatic 4 yr postoperatively. Histologically the VL consisted of many thin-walled channels with spindle-shaped neoplastic cells arranged in fascicles with the nuclei of the cells being vascular with blunt ends. A striking increase of blood vessels with a proliferation of smooth muscle cells in the walls of some of the blood vessels was observed. No mitotic figures were noted. With trichrome stain the elongated spindle-shaped cells were reddish in color, suggesting smooth muscle. (11 Refs)

26. JAUNDICE: DRUGS THAT CAN CAUSE ICTERUS.

Zimmerman HJ
George Washington Univ. Sch. Medicine, Washington, DC
Consultant; 22(2):76-79,83-85,89 1982

Drug-induced jaundice which results from direct injury to hepatocytes is discussed. Such injury is reviewed with a discussion of mechanisms of action, effecting drugs according to therapeutic application, and treatment of drug-induced lesions. Many drugs used in oncotherapy produce steatosis, necrosis, or degeneration of cells or hepatocanalicular cholestasis. Benign liver cell adenoma, malignant hepatocellular carcinoma, and hepatic angiosarcoma are caused by such drugs as anabolic and contraceptive steroids, thorotrast, vinyl chloride, and inorganic arsenic. (3 Refs)

27. RISK FACTORS FOR CERVICAL CANCER.

Hulka BS
Dept. Epidemiology, Rosenau Hall 201H, Univ. North Carolina, Chapel Hill, North Carolina, NC, 27514
J Chronic Dis; 35(1):3-11 1982

Despite a long history of research into the epidemiology and biology of cervical carcinoma, a definitive statement about its probable causes still remains elusive. This review recognizes the population based data on high and low risk groups and summarizes the findings from numerous case-control studies which are associated with cervical cancer. Although vigorously pursued, an increased risk from oral contraceptives has not been convincingly demonstrated. A variety of venereally transmitted organisms appear to be frequent cohabitants with cervical neoplastic cells. Herpesvirus type 2 still remains the prime suspect in the complex pathogenesis of cervical neoplasia. Clinical findings, biological characteristics of the virus, serological studies and interactions of host cells and viral particles continue to stimulate the most intensive investigative efforts. (Author abstract) (69 Refs)

28. HORMONES AND BREAST CANCER.

Pike MC, Silteri PK, Welsch CW
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep 8: 491 pp., 1981.

Sessions held to discuss the relationship between hormones and breast cancer (BC) consisted of the following topics: review of BC epidemiology (as it relates to menarche, pregnancy, and menopause, body size and BC risk), endocrinology of women at risk of BC (hormone profiles in young women at risk of BC with analysis of ovarian function during theelarche, menarche, and menopause, and after childbirth, endocrine maturation during female puberty, reproductive endocrinology and BC in women, increased availability of serum estrogens in BC), review of studies attempting to establish endogenous hormones as important in human BC (estrogens, progesterone, and prolactin in human BC, prospective study of relation between thyroid function and BC, and abnormal plasma hormone levels in women with BC), in vitro studies of human breast tissue (hormonal regulation of human BC cells in vitro, prolactin, pituitary hormones, and BC, estrogen receptor assays in familial and nonfamilial BC), exogenous hormones and BC (epidemiological studies of the role of exogenous estrogens in BC etiology and hormone therapy), other exogenous factors and BC (epidemiological studies of mutagenicity of breast fluids and BC risk, diet and hormone metabolism in BC), hormones and genesis of progression of murine mammary tumors (ovarian steroid hormones, prolactin, growth hormone, insulin, pituitary and steroid hormones, pregnancy and lactation, neuroleptic drugs, and plasma prolactin analysis), and mechanism of hormone action (regulation of casein gene expression in hormone-dependent mammary cancer, control of estrogen-responsive tumor growth, and role of hormones in mammogenesis and carcinogenesis). (453 Refs)

29. PLASMA PROLACTIN ANALYSIS AS A POTENTIAL PREDICTOR OF MURINE MAMMARY TUMORIGENESIS.

Sinha YN, Silteri, Dao TL, Meites J, Rosen JM, Korenman, Shiu, Sirbasku DA
Lutcher Brown Center for Diabetes and Endocrinology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
Banbury Rep; 8:377-394 1981

The correlation between plasma prolactin (PP) and breast cancer (BC) in humans, rats, and mice and possible reasons for the lack of correlation between PP and BC (metabolic clearance rate of prolactin (PR), conversion of PR into nonimmunodetectable forms, size heterogeneity of circulating PR, and immunologically unreactive form of PR in the pituitary) are discussed. A clinical correlation between PP and incidence of BC has not been found, possibly due to a lack of methods for quantification of all different molecular forms of PR present in the blood. (53 Refs)

30. HORMONAL REGULATION OF HUMAN BREAST CANCER CELLS IN VITRO.

Lippman M, Meites J, Welsch CW, Rosen JM, Segaloff A, Koreman SG, Nandi S, Sirbasku DA
Medical Breast Cancer Section, Medicine Branch, NCI, Bethesda, MD, 20205
Banbury Rep; 8:171-184 1981

Cultured breast cancer cell lines (most of which were derived from neoplastic effusions, often after treatment) differ from the original tumors in several important ways. Experiments with these cell lines must be designed and their results interpreted with great caution. Firm conclusions as to the absence of a given hormone response are particularly difficult to interpret. Positive results are much less ambiguous, but these can also give rise to misinterpretations. Nevertheless, the cell-culture approach provides several advantages in the investigation of hormonal interactions with human breast cancer. In particular, drug- and hormone-resistant variants of wild-type parental cell lines can be used to study the mechanisms of hormone dependence. Hormones now known to affect the growth or differentiated functions of human breast cancer cells (especially the MCF-7 cell line) include estrogens, glucocorticoids, androgens, thyroid hormones (the ZR-75-1 cell line is absolutely dependent on physiologic levels of triiodothyronine in the medium, and MCF-7 cells are also thyroid hormone dependent), and insulin. Vitamin A derivatives are required for normal epithelial differentiated and inhibit several types of chemical carcinogenesis in rats. Several human breast cancer cell lines contain separable binding activities for retinol and retinoic acid, but clinical trials of 13-cis-retinoic acid in breast cancer patients have not been encouraging. The roles of epidermal growth factor, vitamin D, progesterone, and prolactin in breast cancer growth are not yet clear. (46 Refs)

31. CELL SURFACE MODULATION IN MAMMARY CANCER.

Thompson K

Bruce Lyon Memorial Res. Lab., Children's Hosp. Medical Center, Oakland, CA, 94609

The Handbook of Cancer Immunology: Volume 8- Tumor Antigens: Structure and Function. Waters H, ed. New York, STPM Garland Press, 418 pp., 1981.

Studies of the cell surface modulation which accompanies malignant transformation in mammary cancer are reviewed. Evidence for cell surface antigens (CSAs) of mouse and rat mammary tumors has not shown whether neoplastic transformation is associated with distinct tumor-specific antigens. Virus-induced mouse mammary tumors contain virus-specific antibodies, which are also present in normal mammary cells and nonmammary tissues. In rats with carcinogen-induced mammary tumors, the tumor loses an organ-specific antigen at the time of spontaneous dissemination. The experimental mammary tumors may also show gene derepression, which leads to the expression of abnormal differentiation antigens and/or fetal-type antigens. The tumors can acquire new CSAs not found in the tissue of origin and can acquire or lose CSAs already present in normal cells. Neoplastic transformation is a complex process, especially with regard to the cells which become neoplastic and the influence of host factors (genetic, hormonal, or immunologic). Interaction of these factors determines the malignant state. (283 Refs)

32. INCREASED AVAILABILITY OF SERUM ESTROGENS IN BREAST CANCER: A NEW HYPOTHESIS.

Siiteri PK, Hammond GL, Nisker JA, Korenman SG, Topp, Bulbrook RD, Henderson BE, Welsch, Meites, Rosen, Lippman, Sirbascu, Petrakis

Reproductive Endocrinology Center, Univ. California, San Francisco, CA, 94143

Banbury Rep; 8:87-106 1981

Mechanism whereby obesity appears to increase the impact of estrogens on target tissue was studied. Measurements of the percentage of free steroids in serum that closely approximates physiologic conditions indicated that estradiol binding to sex-hormone-binding globulin is of potential physiologic importance. Obesity increases target tissue exposure to estrogen, and chronic stimulation of the breast epithelium over a sufficient period of time, may lead to benign breast disease, and set the stage for cancer in those women who are exposed to an effective dose of virus, irradiation, or carcinogens. (58 Refs)

33. 2-BROMO-ALPHA-ERGOCRYPTINE (CB-154) AND TAMOXIFEN (ICI 46,474) INDUCED SUPPRESSION OF THE GENESIS OF MAMMARY CARCINOMAS IN FEMALE RATS TREATED WITH 7,12-DIMETHYLBENZANTHRACENE (DMBA): A COMPARISON.

Welsch CW, Goodrich-Smith M, Brown CK, Mackie D, Johnson D
Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824
Oncology; 39(2):88-92 1982

Daily treatment of female Sprague-Dawley rats with 2-bromo-alpha-ergocryptine (CB-154) (prolactin suppressor) or Tamoxifen (estrogen antagonist) for 33 days before and after 7,12-dimethylbenzanthracene (DMBA) administration reduced (p less than 0.05) the incidence of mammary carcinomas by 58 and 49%, respectively. A combination of CB-154 and Tamoxifen further reduced (p less than 0.05) mammary carcinoma incidence by an additional 50-59%. Treatment with Tamoxifen for 66 days beginning 33 days after carcinogen treatment reduced (p less than 0.05) the incidence of mammary carcinomas by 65%; CB-154 treatment, during the same time period, did not significantly effect the final yield of mammary carcinomas. Th combination of Tamoxifen and CB-154 was comparable to Tamoxifen alone in suppressing the incidence of mammary carcinomas in the latter study. These results demonstrate a substantial suppressive and synergistic effect of Tamoxifen and CB-154 in the initiating phases of mammary carcinogenesis while in the early promoting phases of this oncogenic process, short-term treatment with Tamoxifen was superior to CB-154 treatment; no synergism between these clinically important compounds was observed. (Author abstract) (27 Refs)

34. EFFECT OF RETINYL ACETATE ON THE OCCURRENCE OF OVARIAN HORMONE-RESPONSIVE AND -NONRESPONSIVE MAMMARY CANCERS IN THE RAT.

Thompson HJ, Meeker LD, Tagliaferro AR, Becci PJ
Dept. Home Economics, Univ. New Hampshire, Pettee Hall, Durham, NH, 03824
Cancer Res; 42(3):903-905 1982

The inhibitory activity of retinyl acetate against the induction of ovarian hormone-responsive and -nonresponsive mammary gland adenocarcinomas was studied in intact and castrated female Sprague-Dawley rats. Three experiments were conducted. Mammary cancer was induced by a single po administration of 7,12-dimethylbenz(a)anthracene (DMBA) at 50 days of age. Animals in Experiments 1 and 2 each received 20 mg DMBA, whereas those in Experiment 3 received 15 mg. In all experiments, animals were fed a chow diet supplemented per kg with either a placebo or 328 mg retinyl acetate starting 7 days after carcinogen treatment. In Experiment 1, rats were castrated at either 7, 60, or 90 days postcarcinogen and were killed 120 days after DMBA was given. In Experiment 2, rats were castrated 30 days after DMBA and were killed 240 days after carcinogen treatment. In Experiment 3, rats were castrated when a detected tumor attained a measurable diameter, and the hormone responsiveness of their tumors was subsequently determined. The experiment was terminated 279 days after DMBA treatment. In both intact and castrated rats, mammary tumor occurrence was inhibited by treatment with retinyl acetate. However, there were no differences in the latency to appearance time of hormone-responsive and -nonresponsive cancers in intact animals receiving either placebo or retinyl acetate. The data indicate that retinyl acetate inhibits DMBA-induced mammary tumorigenesis in either the presence or the absence of the ovaries. It appears that retinyl acetate is effective in inhibiting both ovarian hormone-responsive and -nonresponsive mammary tumors. (Author abstract) (15 Refs)

35. INCREASED INDUCTION OF SISTER CHROMATID EXCHANGE BY DIETHYLSTILBESTROL IN LYMPHOCYTES FROM PREGNANT AND PREMENOPAUSAL WOMEN.

Hill A, Wolff S
(c/o Wolff) Lab. Radiobiology and Environmental Health, Dept. Anatomy, Univ. California, San Francisco, CA, 94143
Cancer Res; 42(3):893-896 1982

Cultures of whole blood from pregnant women (4 to 6 mo), premenopausal women, postmenopausal women, and normal men were grown in the presence of varying concentrations (1 x 10(-5) M, 2 x 10(-5) M, and 4 x 10(-5) M) of diethylstilbestrol (DES), a synthetic estrogen and known carcinogen, to see if it had sex-related cytogenetic effects. DES induced sister chromatid exchanges in lymphocytes from pregnant and premenopausal women but had only a small effect at the highest concentration (4 x 10(-5) M) in lymphocytes from men and postmenopausal women. At all concentrations, the av number of sister chromatid exchanges was higher in lymphocytes from pregnant women than in those from premenopausal women. In lymphocytes from both a man and a pregnant woman, DES strongly inhibited cell proliferation in vitro. When lymphocytes from a man and a pregnant woman were cocultured in the presence of DES, only the lymphocytes of the woman responded with an increase in sister chromatid exchanges. This indicated that there is no interaction between DES and a factor present in the blood but that DES acts directly on each cell. (Author abstract) (24 Refs)

36. FECAL STEROID METABOLITES AND BREAST CANCER RISK.

Papatestas AE, Panvelliwalla D, Tartter PI, Miller S, Pertsemlidis D, Aufses AH
Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY, 10029
Cancer; 49(6):1201-1205 1982

Women with breast cancer (n = 78) had a higher excretion of total fecal steroids in mg/gm of dry weight (56 37) compared to controls (45 -29; n = 71) (p = 0.03). Increases in both total neutral steroids and total bile acids in cases contributed to this significant difference. Lean women (Quet elet's index less than 3.5) with breast cancer seemed to have inappropriately high excretion of total fecal steroids (56 -35), which was significantly higher than that of controls (41 -27) (p = 0.03). Obesity resulted in higher excretion of fecal steroids only in controls. The differences persisted, even after pairing control cases for race-ethnicity and menopausal status. In 59 such pairs, cases had higher values (56 -33), compared to controls (41 -26) (p = 0.008). Significant differences (p = 0.005) were also present in 24 post-menopausal pairs, while in 35 pre-menopausal pairs a similar trend, but no significant differences were noted. Women with benign breast disease had higher total fecal steroids (51 -34) compared to the other controls (38 -21) (p = 0.05). This observation suggests a common etiology between benign breast disease and breast cancer. There were no significant differences in dietary intake of total calories, total fat or dietary cholesterol between controls and cases suggesting that the observed differences in fecal steroids could be attributed to higher endogenous synthesis of cholesterol in cases. (Author abstract) (23 Refs)

37. REGULATION OF CASEIN GENE EXPRESSION IN HORMONE-DEPENDENT MAMMARY CANCER.

Rosen JM, Supowit SC, Gupta P, Yu LY, Hobbs AA, Dao TL, Topp, Hilf
Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030
Banbury Rep; 8:397-424 1981

Structure, organization, and expression of the casein gene (CG) family and the alpha-lactalbumin gene in the normal mammary gland, and altered regulation of CG expression and gene expression in general in hormone-dependent mammary cancer, were studied. Milk protein structural genes, hormonal regulation of milk protein messenger RNA accumulation in rat mammary gland organ culture, milk gene organization and chromosomal localization, CG expression in hormone-dependent mammary cancer, methylation patterns of the CG, DNA rearrangement in mammary tumors (MT), and expression of unique single-copy DNA sequences in 7,12-dimethylbenz(a)anthracene-induced MT are reviewed. New approaches may help explain the regulation of differentiated function in the normal mammary gland and deviation of the mechanisms in hormone-dependent breast cancer. (38 Refs)

38. A CHEMICALLY DEFINED MEDIUM FOR THE PROPAGATION OF RAT PROSTATE ADENOCARCINOMA CELLS.

Chan SY
Lobund Lab., Univ. Notre Dame, South Bend, IN, 46556
Prostate; 2(3):291-298 1981

A serum-free growth medium, MB-DF, consisting of a modified Waymouth's MB-752/1 medium supplemented with fetuin (150 ug/ml), insulin (5 ug/ml), transferrin (25 ug/ml), dexamethasone (100 nanog/ml), 5alpha-dihydrotestosterone (100 nanog/ml), NaHCO3 (1.1 mg/ml), penicillin (100 units/ml), and streptomycin (100 ug/ml) was developed and successfully tested with rat prostate adenocarcino ma cell line PA-III derived from aging Lobund Wistar rats. The 95th passage of PA-III was adapted to culture by gradually decreasing the amount of fetal bovine serume (FBS) in the medium from 10% to zero. The adapted cell line PA-IIIf, stored up to 12 mo at-70 C, still exhibited excellent recovery of viable propagating cells. PA-IIIf cells retained the same tumorigenicity as the parent line, and metastasized via the same ipsilateral lymphatic pathway from the footpad to the lungs, in which they produced distinct metastatic foci. (21 Refs)

39. INHIBITION OF THE R3327MAT-LU PROSTATIC TUMOR BY DIETHYLSTILBESTROL AND 1,2-BIS(3,5-DIOXOPIPERAZIN-1-YL)PROPANE.

Lazan DW, Heston WD, Kadmon D, Fair WR
(c/o Heston) Div. Urology, Dept. Surgery, Washington Univ. Sch. Medicine, St. Louis, MO, 63110
Cancer Res; 42(4):1390-1394 1982

We have previously described the inhibitory effects of diethylstilbestrol on the growth of the androgen-independent, anaplastic Copenhagen rat prostatic tumor, R3327AT, which has a low metastatic potential. We have now selected a variant of the R3327AT tumor that metastasizes exclusively to the lungs, and we have designated it the R3327MAT-Lu. In a dose-response protocol, diethylstilbestrol was inhibitory to the primary R3327MAT-Lu tumor, thereby also inhibiting the formation of lung metastases. Inhibition was also observed in this model tumor by the chemotherapeutic agent 1,2-bis(3,5-dioxopiperazin-1-yl)propane. (Author abstract) (23 Refs)

40. SITE-SELECTIVE GROWTH OF A HORMONE-RESPONSIVE HUMAN BREAST CARCINOMA IN ATHYMIC MICE.

White AC, Levy JA, McGrath CM
Dept. Tumor Biology, Michigan Cancer Foundation, Detroit, MI, 48201
Cancer Res; 42(3):906-912 1982

MCF-7 is a human breast cancer line which requires estradiol supplementation for growth in sc tissues of athymic mice. In order to evaluate the influence of host site on hormone-dependent tumorigenicity and growth, MCF-7 cells were inoculated into tissues varying in ability to concentrate exogenous estradiol. Tumorigenicity was defined in terms of latency, threshold inoculum size, and tumor growth and progression. We observed that sites such as lung rarely supported MCF-7 tumors. However, moderately estrophilic sites such as mammary fat and adjacent subcutaneum and dermis supported the growth of small MCF-7 tumors from large tumor cell inocula, but only in estrogenized mice. In contrast, the highly estrophilic sites, brain and periuterine tissues, produced rapidly growing tumors from small cell inocula. Only in periuterine tissues did tumors develop in the absence of exogenous estradiol. These studies demonstrate that tumorigenicity and growth rates of estrogen-dependent MCF-7 tumors vary as a function of tissue implantation site. (Author abstract) (46 Refs)

41. HORMONAL INDUCTION OF CASEIN GENE EXPRESSION LIMITED TO A SMALL SUBPOPULATION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMOR CELLS.

Supowit SC, Rosen JM
(c/o Rosen) Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030
Cancer Res; 42(4):1355-1360 1982

In the hormonally responsive 7,12-dimethylbenz(a)anthracene (DMBA)- or N-nitrosomethylurea (NMU)-induced mammary carcinomas, regulatory mechanisms have been altered such that these tumors retain their hormonal dependence for growth but possess only a limited ability to synthesize the mammary gland-specific milk proteins. Quantitation of casein mRNA levels revealed that very low levels of casein messenger RNA (mRNA) were expressed in both the DMBA- and NMU-induced tumors growing in virgin animals (0.1 to 0.4% of the maximally induced 8-day-lactating mammary gland). Growth of DMBA-induced tumors in pregnant rats and the treatment of NMU-induced tumor-bearing animals with thioproperazine indicated that the tumor casein mRNA levels were hormone inducible (3.4-and 2.1-fold for the DMBA- and NMU-induced tumors, respectively). However, casein mRNA levels were still only 1 to 2% of those found in the normal mammary gland under the same hormonal environment. Localization of the casein-synthesizing cells in the DMBA-induced tumors by peroxidase-antiperoxidase staining and a specific casein antiserum indicated that, in both control and hormone-treated tumors, the vast majority of cells (greater than 95%) were unable to synthesize casein. The hormonal induction of casein mRNA sequences could be correlated with an increase in the number of cells synthesizing casein, which appeared as small clusters of cells throughout the tumors. Therefore, the loss of hormone-regulated differentiated function in these tumors, which maintained hormone-dependent growth, suggests the presence of a defective regulatory mechanism beyond the level of the hormone-receptor complex. (Author abstract) (29 Refs)

42. SPECIFIC HIGH AFFINITY BINDING SITES FOR SOMATOSTATIN-28 ON PANCREATIC BETA-CELLS: DIFFERENCES WITH BRAIN SOMATOSTATIN RECEPTORS.

Reubi JC, Rivier J, Perrin M, Brown M, Vale W
Peptide Biology Lab., Salk Inst., P.O. Box 85800, San Diego, CA, 92138
Endocrinology; 110(3):1049-1051 1982

Saturable and high affinity binding sites have been obtained for an iodinated somatostatin-28 (SS-28) analog, [Leu8,D-Trp22,125I-Tyr25] SS-28, in a membrane preparation from hamster insulinoma, mainly composed of pancreatic beta-cells. Specific binding is maximal after 1 hr incubation at 22 C and represents 65% of the total binding. KD for [Leu8,D-Trp22,Tyr25] SS-28 is 0.25 nM with the number of sites corresponding to 68 fmol/mg protein. The Kd for SS-28 (1 nM) is more than 5 times lower than that for SS-14. SS-28 analogs, such as [D-Trp22] SS-28 and analogs which selectively inhibit insulin release in vivo (Des-Asn5[D-Trp8,D-Ser13] SS-14 and Des-Asn19[D-Trp22,D-Ser27] SS-28), are the most potent compounds in this assay. C-terminal replacement of L-cysteine by D-cysteine reduces the apparent affinity of SS analogs. Unrelated peptides and the inactive analog Des-Trp8-SS-14 have no affinity for insulinoma binding sites. There are differences between the insulinoma SS binding sites and those monitored under similar conditions from rat cerebral cortex. In cerebral cortex, SS-14 and SS-28 have similar affinity for the binding sites, and the insulin selective analogs are less potent than SS-14. It is concluded that pancreatic beta-cells, as well as brain, possess high affinity binding sites for SS, but that they differ in some of their pharmacological properties. (Author abstract) (16 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Andre F. 11
Aufses AH. 36
Becci PJ. 34
Bouton MM. 13
Briggs M. 24
Briggs MH. 24
Brown CK. 33
Brown JB. 5
Brown M. 42
Budisic Z. 9
Bulbrook RD. 1
Bulbrook RD. 32
Bulbrook RD. 4
Bulic N. 9
Caldwell GG. 7
Chan SY. 38
Cole. 17
Cole P. 3
Cole P. 4
Cole P. 6
Cook B. 12
Cotard M. 11
Crowley S. 7
Dallenberg-Hell. 2
Dao TL. 17
Dao TL. 20
Dao TL. 29
Dao TL. 37
Degen GH. 14
Eckelman WC. 12
Edwards AM. 15
Eling TE. 14
Fair WR. 39
Falk H. 7
Frensilli JA. 22
Gamulin S. 9
Garbaczewski L. 6
Gibson RE. 12
Goodrich-Smith. 33
Grandadam JA. 13
Gupta P. 37
Guzman R. 23
Hammond GL. 32
Helman P. 6
Henderson BE. 1
Henderson BE. 17
Henderson BE. 20
Henderson BE. 32
Henderson BE. 4
Henderson BE. 5
Henderson BE. 6
Hendley R. 16
Herbert J. 7
Heston WD. 39
Hilf. 37
Hill A. 35
Hill P. 6
Hobbs AA. 37
Hulka BS. 27
Ishak KG. 7
Johnson D. 33
Kadmon D. 39
Kasumi F. 6
Kelsey JL. 1
Korenman. 29
Korenman SG. 1
Korenman SG. 23
Korenman SG. 30
Korenman SG. 32
Korenman SG. 6
Kosovel E. 9
Kubovic M. 9
Kuno K. 6
Lazan DW. 39
Levy JA. 40
Li JJ. 10
Li SA. 10
Lin YC. 21
Lippman. 32
Lippman M. 30
Loring JM. 21
Mackie D. 33
Martin PM. 11
Martinac P. 9
McGrath CM. 40
McLachlan JA. 14
Meeker LD. 34
Meites. 32
Meites J. 20
Meites J. 29
Meites J. 30
Meites J. 4
Mialot JP. 11
Miller S. 36
Montani Dj. 9
Moon. 17
Moon RC. 20
Moon RC. 4
Nandi S. 23
Nandi S. 30
Naranck P. 9
Nisker JA. 32
Oates KK. 12
Panvelliwalla D. 36
Papatestas AE. 36
Perrin M. 42
Pertsemlidis D. 36
Petrakis. 32
Pieslor PC. 12
Pike MC. 20
Pike MC. 28
Pike MC. 4
Pike MC. 5
Pike MC. 6
Popper H. 7
Pornin C. 13
Raynaud JP. 11
Reba RC. 12
Reubi JC. 42
Richards J. 23
Rivier J. 42
Rolland PH. 11
Rosen. 32
Rosen JM. 23
Rosen JM. 29
Rosen JM. 30
Rosen JM. 37
Rosen JM. 41
Saez S. 8
Segaloff. 17
Segaloff A. 30
Segaloff A. 4
Segaloff A. 6
Shellabarger CJ. 19
Shellabarger CJ. 20
Shellabarger CJ. 23
Shellbarger CJ. 4
Shiu. 29
Siiteri. 29
Siiteri. 5
Siiteri PK. 1
Siiteri PK. 23
Siiteri PK. 28
Siiteri PK. 32
Siiteri PK. 4
Sinha YN. 20
Sinha YN. 29
Sirbascu. 17
Sirbascu. 32
Sirbasku DA. 23
Sirbasku DA. 29
Sirbasku DA. 30
Sirbasku DA. 6
Stojkovic R. 9
Supowit SC. 37
Supowit SC. 41
Tagliaferro AR. 34
Tartter PI. 36
Thomas LB. 7
Thompson HJ. 34
Thompson K. 31
Topp. 32
Topp. 37
Topp W. 6
Tsoutsouris GV. 25
Unusic J. 9
Vale W. 42
Villee CA. 21
Weatherred JG. 22
Welsch. 32
Welsch CW. 17
Welsch CW. 18
Welsch CW. 28
Welsch CW. 30
Welsch CW. 33
White AC. 40
Williams MT. 16
Wolff S. 35
Wynder EL. 6
Yang J. 23
Yu LY. 37
Zimmerman HJ. 26
Zumoff B. 6
Zumoff BJ. 17

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CHEMICAL CARCINOGENESIS

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Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
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Madewell BR

Section Clinical Oncology, Dept. Veterinary Surgery, Univ. California, Davis, CA, 95616

Yale J Biol Med; 54(2):111-125 1981

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ICRDB CANCERGRAM

HORMONAL CARCINOGENESIS

SERIES CK05 No. 82/08

AUGUST, 1982

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In this issue:

- **ORAL CONTRACEPTIVES AND HUMAN CANCER** 1-4
- **ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER** 5-9
- **MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES** 10
- **HORMONAL CARCINOGENESIS IN ANIMALS** 11-12
- **REVIEWS AND OTHER RELATED STUDIES** 13-16

ORAL CONTRACEPTIVES AND HUMAN CANCER

1. THE MORPHOLOGIC RESPONSE OF THE HUMAN ENDOMETRIUM TO LONG-TERM TREATMENT WITH PROGESTATIONAL AGENTS.

Ludwig H
Dept. Obstetrics and Gynecology, Univ. Essen, Hufelandstrasse 55, 4300 Essen 1, W. Germany

Am J Obstet Gynecol; 142(6,part2):796-808 1982

The effects of progestational agents on the human endometrium are masked by the proliferating action of endogenous estrogens or by an estrogen compound used for oral contraception. It is therefore difficult to describe the morphology of the endometrial reaction caused by progestational agents alone. The endometria of 12 women were examined, 11 of whom

HE20. 3173/2:

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were on a long-term, low-dose regimen of progestogens for contraception; the 12th was on a short-term, high-dose regimen of injectable progestogen for adjuvant therapy of breast cancer. Endometria from the patients were evaluated with respect to the following parameters: gland mitoses, gland tortuosity, pseudostratification, basal vacuolation, signs of secretion, stromal edema, predecidual reaction, and leukocytic infiltration. The morphologic examination was performed with the light microscope using different stainings and with the scanning electron microscope. (Author abstract) (15 Refs)

2. NONCONTRACEPTIVE HEALTH BENEFITS OF ORAL STEROIDAL CONTRACEPTIVES.

Mishell DR
Dept. Obstetrics and Gynecology, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Am J Obstet Gynecol; 142(6,part2):809-816 1982

Prospective and retrospective epidemiologic studies involving oral contraceptives have been reviewed to determine the existence and extent of their benefits other than prevention of pregnancy. There is less menstrual blood loss, which reduces the risk of iron deficiency anemia by about 50%. The incidence of menorrhagia, irregular menses, and intermenstrual bleeding is also significantly reduced in users of oral contraceptives. Studies have shown an approx 50% reduction in risk of endometrial cancer in oral contraceptive users, as well as a significant reduction in various types of benign breast disease. Because oral contraceptives inhibit ovulation, functional ovarian cysts are nearly eliminated, and the incidence of dysmenorrhea and premenstrual tension is significantly reduced. Oral contraceptives also protect women from developing ovarian carcinoma, rheumatoid arthritis, and salpingitis. From this review we conclude that the benefits of oral contraceptives in young healthy women far outweigh their more widely publicized, infrequent risks. (Author abstract) (22 Refs)

3. BREAST CANCER AND THE PILL. NO CLEAR EVIDENCE OF AN ASSOCIATION HAS YET BEEN DEMONSTRATED.

Fraser IS
No affiliation given
Med J Aust; 1(1):6 1982

Despite suggestions of a relationship between use of oral contraceptives and breast cancer, two recent cohort studies and a matched control study have shown no consistent significant increase or decrease in the risk of breast cancer between any group of oral contraceptive users and their controls. The possible risk for young women using the Pill for many yr before their first pregnancy is considered. Problems associated with studying the long-term risks of the Pill are discussed. (10 Refs)

4. ROLE OF HORMONES IN THE ETIOLOGY AND PREVENTION OF ENDOMETRIAL AND BREAST CANCER.

Gambrell RD
Dept. Endocrinology, Medical Coll. Georgia, Augusta, GA, 30912
Acta Obstet Gynecol Scand [Suppl]; (106):37-46 1982

Although there is a slightly increased risk of endometrial cancer from estrogen therapy for menopausal women, progestogens given along with the estrogen significantly decrease the incidence of this malignancy to a rate lower than that of untreated women. Postmenopausal women predisposed to adenocarcinoma of the endometrium because of increased endogenous estrogens can be identified with the progestogen challenge test and treated with cyclic progestogens for 10 days each mo to prevent endometrial cancer. Oral contraceptives containing both estrogens and progestogens in each tablet are protective against developing adenocarcinoma of the endometrium, whereas the sequential birth control pills provided less protection. The incidence of breast cancer is significantly lower in both estrogen and estrogen-progestogen users than in postmenopausal women never using these hormones. In those women found to have breast cancer while using these hormones, the prognosis is better than that found in women never exposed to exogenous estrogens, most likely due to an earlier detection. No clear-cut pattern of either abnormal hormone production or milieu has been found in women with carcinoma of the breast. Oral contraceptives reduce the risk of benign breast disease and afford some protection from the subsequent development of breast cancer. The mortality rate from breast cancer developing in oral contraceptive users is significantly lower than that of the non-users. (Author abstract) (50 Refs)

ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER

5. DIET AND HORMONE PROFILES IN TEENAGE GIRLS IN FOUR COUNTRIES AT DIFFERENT RISK FOR BREAST CANCER.

Gray GE, Pike MC, Hirayama T, Tellez J, Gerkins V, Brown JB, Casagrande JT, Henderson BE
(c/o Henderson) Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA, 90033
Prev Med; 11(1):108-113 1982

Findings on diet and possible breast cancer risk factors in adolescent girls in Chile (CH), Japan (JA), Papua New Guinea (PNG), and the United States (US) are presented. The 51 CH girls (mean age 17.0 yr), 50 JA girls (mean age 16.9 yr), and 68 PNG girls (mean age 17.7 yr) were from rural areas, and the 50 US girls (mean age 16.5) were all members of the same church. The subjects were postmenarchial with an av cycle of 26-32 days and had never been pregnant or used oral contraceptives or other medication known to influence sex hormone levels (SHL). Blood samples were to be collected in the morning not less than 30 min after the subject awakened on day 11 of the menstrual cycle; the condition was achieved for all girls except for 32% of CH girls. Obvious differences in body build among the subjects from the countries were noted. Dietary data and mean SHL are presented. The only significant differences were in urinary estriol and the urinary estriol ratio. The levels were considerably higher in PNG girls than in those from girls from the other three countries. Correlation coefficients were calculated to assess the relationship between anthropometric measurements, age, age at menarche, percentage of calories from fat, carbohydrate, and protein, and SHL within each country. No consistent relationship between SHL and any of the other factors were found. The anthropometric measurements and age at menarche were not related to the dietary variables within each country. According to the results, at least with diets leading to the same age at menarche, an increased percentage of calories from fat does not increase prolactin levels. (24 Refs)

HE20. 3173/2:

6. ON THE ROLE OF ESTROGENS IN ENDOMETRIAL CARCINOGENESIS.

Astedt B
Dept. Obstetrics and Gynecology, Univ. Hosp., S-221 85 Lund, Sweden
Acta Obstet Gynecol Scand [Suppl]; (106):33-35 1981

The role of estrogen in endometrial carcinoma as a carcinogenic agent or as a promoter is discussed. Dosage level, duration of treatment, and formula of preparations must be considered when investigating the role of estrogens in development of endometrial cancer. The observation that the risk declines after cessation of estrogen treatment argues for a promoter effect of estrogens. The antipromoter effect of progestogens is discussed. (30 Refs)

7. MELANOMA OF THE SKIN: SOME EPIDEMIOLOGICAL ASPECTS.

Green A
Queensland Inst. Medical Res., Australia
Aust Fam Physician; 11(1):7-12 1982

Epidemiological aspects of melanoma of the skin are reported. The incidence and mortality rate of cutaneous melanoma is increasing in several countries. Types of melanoma include Hutchinson's melanotic freckle, superficial spreading melanoma, nodular melanoma, and acral lentiginous melanoma. Sun exposure is causally related to melanoma and depends on latitude, skin pigment, and body site exposed. Other etiological factors include hormones, socioeconomic status, and heredity. Current preventive concepts include awareness of characteristics of UV radiation, protective clothing, and use of sunscreens. (29 Refs)

8. ONCOLOGICAL ASPECTS OF SCLEROCYSTIC OVARY SYNDROME.

Bokhman IaU, Vishnevskii AS, Umenushkina LN, Anisimov VN
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Akush Ginekol (Mosk); (2):19-21 1982

Role of sclerocystic ovary syndrome (SCOS) in the etiology of hyperplasia and cancer of the endometrium is discussed. Development of hyperplastic changes in the endometrium is associated with enhanced estrogenic stimulation of the uterine mucosa. It was recommended to include the patients with all variants of SCOS into high risk group. The patients with SCOS should undergo two-stage treatment consisting of progestagen and agents that stimulate ovulation and normalize the menstrual cycle. (5 Refs) (In RUS)

9. PSEUDOSARCOMA BOTRYOIDES OF THE VAGINA IN PREGNANCY.

O'Quinn AG, Edwards CL, Gallager HS
Div. Gynecologic Oncology, Dept. Obstetrics and Gynecology, Tulane Univ. Sch. Medicine, 1430 Tulane Ave., New Orleans, LA, 70112
Gynecol Oncol; 13(2):237-241 1982

Polypoid masses that protrude into the vaginal canal always raise the suspicion of sarcoma botryoides. It is our purpose to report a case of the benign vaginal polypoid lesion, pseudosarcoma botryoides, and to review the literature concerning this lesion. Hormonal milieu appears to play a role in their etiology. The criteria for distinguishing benign vaginal polyp from sarcoma botryoides and mixed mesodermal sarcoma are discussed. (Author abstract) (6 Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES

10. ASSAY OF ESTRADIOL RECEPTORS IN HUMAN BREAST CARCINOMAS USING THE GAMMA EMITTING LIGAND 16ALPHA[125I]IODOESTRADIOL.

Duffy MJ
Dept. Nuclear Medicine, St. Vincent's Hosp., Dublin 4, Ireland
J Steroid Biochem; 16(2):343-344 1982

The use of 16alpha[125I]iodoestradiol to assay estrogen receptor (ER) in human breast carcinoma was investigated. A constant amount of cytosol was incubated at five different concentrations of radiolabeled estradiol overnight at 4 C, and nonspecific binding was measured with parallel incubations in the presence of 100-fold excess unlabeled diethylstilbestrol (DES). Excess unlabeled estradiol and DES were the most potent inhibitors of binding, estrone and estriol were less potent, and testosterone, progesterone, and cortisol were ineffective. The affinity of iodoestradiol for breast tumor ER was similar to that of tritiated estradiol in 19 carcinoma cytosols. Good agreement was found between results using tritiated and iodoestradiol as ligands (correlation coefficient = 0.97). Twelve tumors contained less than 50 femtomoles ER by both ligands. Good agreement was observed between the use of a single saturating concentration of 5 nanoM iodoestradiol and the Scatchard plot analysis using the same ligand (correlation coefficient = 0.97). Advantages of using a gamma-emitting ligand for the assay of ER in breast tumor tissue are listed. (4 Refs)

HORMONAL CARCINOGENESIS IN ANIMALS

11. SEX HORMONES AND LIVER CANCER.

Williams GM
Naylor Dana Inst. for Disease Prevention, New York Medical Coll., Valhalla, NY
Lab Invest; 46(3):352-354 1982

The ability of hormones to produce tumors in endocrine-related organs of experimental animals and the phenomenon of two-stage carcinogenesis is reviewed. Liver tumor promotion, mechanisms of promotion, and the potential impact of use of estrogen-containing drugs on cancer development are discussed. The fact that human exposure to several promoters (eg phenobarbital and dichlorodiphenyl trichloroethane) does not appear to cause increased occurrence of liver neoplasms may mean that the agents were not present at high levels or for prolonged continuous exposure sufficient to impede cell-cell communication and thus promoting activity. (41 Refs)

12. ROLE OF ESTROGENS AS PROMOTERS OF HEPATIC NEOPLASIA.

Wanless IR, Medline A
Dept. Pathology, Toronto Western Hosp., Toronto, Ontario, Canada
Lab Invest; 46(3):313-320 1982

The administration of estrogens to humans has been associated with the development of benign and possibly malignant hepatocellular neoplasms. This study was designed to investigate the mechanism of this association. We present a rat model that demonstrates that stilbestrol (DES) and ethinyl estradiol promote the development of hepatic neoplasms in rats previously initiated with diethylnitrosamine (DEN). Eighty male and 12 female Fischer-344 rats were given a single intraperitoneal injection of either DEN (200 mg/kg of body wt) or saline. Beginning 4 wk after injection, the rats were given an estrogen or corn oil twice weekly for up to 50 wk. Treatments were stopped at the time of sacrifice or 11 to 29 wk prior to sacrifice. Estrogen treatments included high dose DES (5 mg per dose), low dose DES (0.5 mg per dose), and ethinyl estradiol (0.2 mg per dose). Male and female rats given both DEN and high dose of DES developed grossly visible hepatic hyperplasic nodules (mean, 9.1 per liver) after 20 wk of DES. Nodules also developed if the onset of DES treatment was delayed until 28 wk after initiation. Rats given DEN alone or DES alone did not develop nodules after 20 wk. Microscopic hyperplastic foci also developed in rats given DEN plus DES, DES alone, and DEN alone. The foci in rats given DES alone were largely reversible on cessation of estrogen therapy. Mitotic activity in foci and nodules was prominent during estrogen therapy but declined markedly after cessation of therapy. Similar promoting activity of ethinyl estradiol was observed. Low dose DES was not effective in promoting tumor formation. The data indicate that estrogens promote hepatic neoplasia, perhaps by increasing hepatocyte mitotic activity and thereby facilitating the evolution of previously initiated cells into neoplastic clones. Comparison with human disease should be made with caution, especially because the estrogenic dose administered was approx 200-fold the usual contraceptive dose in humans. However, the analogy between this model and the development of human oral contraceptive-associated hepatic tumors is evident. It is possible that some women have latent 'initiated' cells that divide faster than the surrounding hepatocytes in response to estrogens. (Author abstract) (29 Refs)

REVIEWS AND OTHER RELATED STUDIES

13. SEX HORMONES AND RELATED COMPOUNDS, INCLUDING ORAL CONTRACEPTIVES.

Plotz EJ, Nocke W, Schander K, Patt V, Kaulhausen H
Dept. Obstetrics and Gynecology, Univ. Bonn, 5300 Bonn-Venusberg, W. Germany
Side Eff Drug Annu; (5):358-380 1981

Side effects of sex hormones and related compounds are reviewed. Hormonal replacement therapy is discussed with respect to conjugated estrogens, estrogen/progestogen combinations, estriol succinate, estradiol valerate, a combination of the two preceding drugs, intravaginally administered estrogens, and benefits vs risks. Treatment with sex hormones of breast and liver tumors, industrial exposure to steroid hormones used in oral contraceptives (OC), gall bladder disease, psychic changes, acute intermittent porphyria, prolactin secretion in cases of pituitary adenoma and in lactating women, injectable and implanted steroidal contraceptives, low-dose combination OC, progestogen-only OC, combination of estrogens with cyproterone acetate, hormonal contraceptives and vitamins, teratogenicity, antiestrogens, and antiandrogens are each discussed. (159 Refs)

14. CURRENT CANCER RESEARCH ON PEDIATRIC NEOPLASMS (SPECIAL LISTING).

International Cancer Research Data Bank Program Office
NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Pediatric Neoplasms (Special Listing) This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-929411:; 52pp. 1981

Special Listings of Current Cancer Research Projects are a service of the International Cancer Research Data Bank (ICRDB) program of the National Cancer Institute. Each listing contains descriptions of ongoing projects in one selected cancer research area. The descriptions are provided by cancer scientists in about 50 different countries. Etiological and epidemiological studies of pediatric neoplasms are discussed with respect to familial, genetic and congenital factors and the incidence of childhood cancer; in utero exposure to exogenous estrogens and other agents and the incidence of childhood cancer; iatrogenic exposure to radiation and drugs and the incidence of childhood cancer; demographic and other etiologic factors and the incidence of pediatric leukemia, lymphoma, nephroblastoma, and other solid tumors; and other environmental and etiologic factors. Preclinical chemotherapy studies in model systems of pediatric neoplasms are desribed. Clinical diagnosis and prognostic factors in childhood cancer are discussed. Therapy of leukemia, lymphoma, histiocytosis, intracranial tumors, neuroblastoma, nephroblastoma, retinoblastoma, rhabdomyosarcoma, and other solid tumors is outlined and pharmacokinetics, therapeutic complications, and patient supportive care are discussed. Clinical studies by cooperative groups, broad clinical programs, and educational programs are reviewed.

15. CANCER. AN INTRODUCTION.

Creasy WA
Dept. Pharmacology, Univ. Pennsylvania Sch. Medicine, Philadelphia, PA
Cancer. An Introduction. New York, Oxford University Press, 271 pp., 1981.

Nature and incidence of cancer (CA), the features of CA growth and metastasis, the biological interactions between the tumor and the host, the principles of diagnostic approaches, the various factors known or suspected to produce CA, the forms of treatment, and some of the major directions of CA research are presented. Classification of tumors and growth disorders, grades and stages, differentiation, dedifferentiation, and mutation are discussed. Comparative neoplasia, historical aspects of human CA, modern incidence and trends in incidence of CA, and probability of developing CA are reviewed. Host-tumor relationships as manifested in cachexia, pain, hormonal and other humoral factors, psychological aspects, and miscellaneous complaints are considered. Detection and diagnosis of CA consist of self-examination, surgical and cytological diagnosis, radiological tests, direct inspection of lesions, biochemical diagnostic tests, and immunological diagnosis. The etiology of CA includes genetic factors in CA development, psychological, immunological, endocrinological, and metabolic aspects of CA development, chemical, radiation, and miscellaneous mechanisms of carcinogenesis, and viral etiology of CA. Surgery, radiotherapy, chemotherapy, and immunotherapy are used in CA treatment. Unproven and dietary treatments for CA are those with laetrile, dietary regimens, vitamin therapy, and some other unproven and folk remedies. The CA research endeavor in drug development, clinical trials, and some recent areas of research activity in therapeutics are reviewed. (710 Refs)

16. INDUCTION OF SISTER-CHROMATID EXCHANGES BY INDIRECT MUTAGENS/CARCINOGENS IN CULTURED RAT HEPATOMA AND ESOPHAGEAL TUMOR CELLS AND IN CHINESE HAMSTER DON CELLS CO-CULTIVATED WITH RAT CELLS.

Abe S, Sasaki M
(c/o Sasaki) Chromosome Res. Unit, Faculty Science, Hokkaido Univ., North 10, West 8, Sapporo, Hokkaido 060, Japan
Mutat Res; 93(2):409-418 1982

The inducibility of sister-chromatid exchanges (SCEs) in rat ascites hepatoma (AH66-B) and a rat esophageal tumor (R1) cell lines by 2-acetylaminofluorene, butylbutanolnitrosamine, cyclophosphamide, urethane, 4-aminoazobenzene, 2-methyl-4-dimethylaminoazobenzene, 3'-methyl-4-dimethylaminoazobenzene, 4-o-tolyazo-o-toluidine, benzo(a)pyrene, 7,12-dimethylbenzyl(a)anthracene, 3-methylcholanthrene, and diethylstilbestrol (DES) was studied. Six of the chemicals were used with a cell-mediated system using Chinese hamster Don-6 cells as the target cells and co-cultivated AH66-B or R1 cells as the metabolizing feeder layer. Out of 14 indirect mutagens/carcinogens tested, 11, including 5 amine derivatives, 3 azo compounds, 2 aromatic hydrocarbons and 1 steroid, induced SCEs in AH66-B and/or R1 cells. The frequency of SCEs in Don-67 cells exposed to 6 selected chemicals was substantially enhanced in the presence of AH66-B or R1 cells. For some chemicals, especially aromatic hydrocarbons, the doses required to induce SCEs in AH66-B and R1 cells were much higher than those reported for some other cell systems. Certain chemicals, eg, DES, were active inducers of SCEs in the present systems, but are known to be inactive in microbial and other test systems. The two approaches described represent simple and reliable screening assays in vitro for detection of indirect mutagens/carcinogens. (32 Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Abe S. 16
Anisimov VN 8
Astedt B. 6
Bokhman IaU 8
Brown JB 5
Casagrande JT 5
Creasy WA 15
Duffy MJ 10
Edwards CL 9
Fraser IS 3
Gallager HS 9
Gambrell RD 4
Gerkins V 5
Gray GE 5
Green A 7
Henderson BE 5
Hirayama T 5
International C 14
Kaulhausen H 13
Ludwig H 1
Medline A 12
Mishell DR 2
Nocke W 13
O'Quinn AG 9
Patt V 13
Pike MC 5
Plotz EJ 13
Sasaki M 16
Schander K 13
Tellez J 5
Umenushkina LN 8
Vishnevskii AS 8
Wanless IR 12
Williams GM 11

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY AND METABOLISM OF ACRYLONITRILE.
Sapota A, Chmielnicka J
Zaklad Metabolizmu Substancji Toksycznych, Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland
Med Pr; 32(1):25-33 1981
In POL

2. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.
Combes RD, Haveland-Smith RB
Dept. Biological Sciences, Portsmouth Polytechnic, King Henry I St., Portsmouth, PO1 2DY, Hants, England
Mutat Res; 98(2):101-248 1982

3. CARCINOGENICITY OF AIRBORNE FINE PARTICULATE BENZO(A)PYRENE: AN APPRAISAL OF THE EVIDENCE AND THE NEED FOR CONTROL.
Perera F
Natl. Resources Defense Council, Inc., 122 East 42nd St., New York, NY, 10168
Environ Health Perspect; 42:163-185 1981

4. TOXICOLOGY OF N-NITROSO COMPOUNDS.
Coulston F, Olajos EJ
Albany Medical Coll., Albany, NY, 12208
Ecotoxicol Environ Saf; 6(1):89-96 1982

5. CRITICAL REVIEW OF THE MUTAGENIC AND OTHER GENOTOXIC EFFECTS OF DIRECT COAL LIQUEFACTION.
Kimball RF, Munro NB
Oak Ridge Natl. Lab., Oak Ridge, TN
Critical Review of the Mutagenic and Other Genotoxic Effects of Direct Coal Liquefaction. Available from National Technical Information Service, Springfield, VA, as DE81027859:, 216 pp., 1981.

6. CARCINOGENICITY AND ITS EFFECT ON MEDICINAL RESEARCH PROGRAMS IN THE USA.
Van Ryzin RJ
Pharmaceutical Res. and Development, Sandoz, Inc., East Hanover, NJ, 07936
Med Res Rev; 2(2):153-166 1982

7. ANTIPROTOZOAL DRUGS (SIDE EFFECTS).
Nir I
Dept. Pharmacology and Experimental Therapeutics, The Hebrew Univ., Hadassah Medical Sch., Jerusalem, Israel
Side Eff Drugs Annu; (5):278-284 1981

8. DRUGS USED IN TUBERCULOSIS AND LEPROSY (SIDE EFFECTS).
Elis J
Inst. Pharmacology, Czechoslovak Acad. Sciences, Albertov 4, Prague 2, Czechoslovakia
Side Eff Drugs Annu; (5):290-297 1981

9. SEX HORMONES AND RELATED COMPOUNDS, INCLUDING ORAL CONTRACEPTIVES.
Plotz EJ, Nocke W, Schander K, Patt V, Kaulhausen H
Dept. Obstetrics and Gynecology, Univ. Bonn, 5300 Bonn-Venusberg, W. Germany
Side Eff Drug Annu; (5):358-380 1981

RADIATION CARCINOGENESIS

10. NEPTUNIUM - THE NEGLECTED ACTINIDE: A REVIEW OF THE BIOLOGICAL AND ENVIRONMENTAL LITERATURE.
Thompson RC
Biology Dept., Pacific Northwest Lab., Richland, WA, 99352
Radiat Res; 90(1):1-32 1982

11. CARCINOGENIC EFFECT OF RADIOACTIVE PRODUCTS.
Vasilenko Ila
No affiliation given
Vopr Onkol; 28(1):76-83 1982
In RUS

DIETARY FACTORS IN CARCINOGENESIS

12. FIBRES, NUTRITION AND THE GUT.
Schrijver M, Tytgat GN
Dept. Internal Medicine, Div. Gastroenterology, Univ. Amsterdam, I e Helmerstraat 104, 1054 EG Amsterdam, The Netherlands
Neth J Med; 25(2):49-55 1982

13. DIETARY FIBER AND DISEASE.
Kritchevsky D
Wistar Inst. Anatomy and Biology, Philadelphia, PA
Bull NY Acad Med; 58(3):230-241 1982

14. ASSESSING HUMAN EPIDEMIOLOGIC DATA ON DIET AS AN ETIOLOGIC FACTOR IN CANCER DEVELOPMENT.
Enstrom JE
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Bull NY Acad Med; 58(3):313-322 1982

15. NUTRITION AND CANCER: MECHANISMS OF GENOTOXIC AND EPIGENETIC CARCINOGENS IN NUTRITIONAL CARCINOGENESIS.
Weisburger JH, Horn C
American Health Foundation, Valhalla, NY, 10595
Bull NY Acad Med; 58(3):296-312 1982

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16. THE AH LOCUS, A MULTIGENE FAMILY NECESSARY FOR SURVIVAL IN A CHEMICALLY ADVERSE ENVIRONMENT: COMPARISON WITH THE IMMUNE SYSTEM.
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Adv Genet; 21:1-52 1982

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

17. SKIN CANCER: OCCUPATIONAL CAUSES.
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Dept. Dermatology, Case Western Reserve Univ., Cleveland, OH
Consultant; 22(4):392-393,397,400-401 1982

18. OCCUPATIONAL AND ENVIRONMENTAL HEALTH PROBLEMS OF THE DEVELOPING OIL SHALE INDUSTRY: A REVIEW.
Rom WN, Lee JS, Craft BF
Rocky Mountain Center Occupational and Environmental Health, Dept. Internal Medicine, Family and Community Medicine, Univ. Utah Sch. Medicine, Bldg. 512, Salt Lake City, UT, 84112
Am J Industr Med; 2(3):247-260 1981

19. POLYCYCLIC AROMATIC HYDROCARBONS IN THE OCCUPATIONAL ENVIRONMENT: WITH SPECIAL REFERENCE TO BENZO[A]PYRENE MEASUREMENTS IN SWEDISH INDUSTRY.
Lindstedt G, Sollenberg J
Chemistry Dept., Natl. Board Occupational Safety and Health, S-171 84 Solna, Sweden
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20. GENETIC RISKS AND ENVIRONMENTAL SURVEILLANCE: EPIDEMIOLOGICAL ASPECTS OF MONITORING INDUSTRIAL POPULATIONS FOR ENVIRONMENTAL MUTAGENS.
Buffler PA, Aase JM
Sch. Public Health, Univ. Texas Health Science Center at Houston, P.O. Box 20186, Houston, TX, 77025
JOM; 24(4):305-314 1982

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No affiliation given
San Diego Law Rev; 18(4/5):633-661 1981

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Kotin P
4505 South Yosemite, 339, Denver, CO, 80237
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23. MODIFICATIONS OF CHROMATIN STRUCTURE IN CONTROL OF GENE EXPRESSION.
Hull LA
104 Depot St., New Sharon, IA, 50207
Med Hypotheses; 8(2):113-133 1982

24. PLASMINOGEN ACTIVATORS IN NEOPLASTIC CELLS.
Goloborod'ko OP, Veremeenko KN
A. I. Kolomiichenko Res. Inst. Otolaryngology, Kiev, USSR
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Dept. Pathology, Upstate Medical Center, State Univ. New York, Syracuse, NY, 13210
J Cutan Pathol; 9(1):1-18 1982

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Williams GM
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Lab Invest; 46(3):352-354 1982

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27. UTILIZATION OF CELL TRANSFORMATION TESTS IN THE DETECTION OF CHEMICAL CARCINOGENS.
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Institut National de Recherche, Centre de Recherche de Nancy, avenue de Bourgogne, F-54500 Vandoeuvre-les-Nancy, France
Bull Cancer (Paris); 69(1):33-57 1982
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Clark RL
Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer; 49(9):1739-1745 1982

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HORMONAL CARCINOGENESIS

SERIES CK05 No. 82/09

SEPTEMBER, 1982

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In this issue:

- **ORAL CONTRACEPTIVES AND HUMAN CANCER** 1-2
- **ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER** 3-5
- **MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES** 6-7
- **MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES** 8-11
- **HORMONAL CARCINOGENESIS IN ANIMALS** 12-13
- **REVIEWS AND OTHER RELATED STUDIES** 14-15

ORAL CONTRACEPTIVES AND HUMAN CANCER

1. ORAL CONTRACEPTIVE USE AND MALIGNANT MELANOMA.

Bain C, Hennekens CH, Speizer FE, Rosner B, Willett W, Belanger C (c/o Hennekens) Channing Lab., 180 Longwood Ave., Boston, MA, 02115
JNCI; 68(4):537-539 1982

There was no overall relationship between a prior history of oral contraceptive (OC) use and the development of melanoma

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

among 141 cases of nonfatal malignant melanoma and 2,820 age-matched controls drawn from respondents to a large postal survey of registered US nurses; crude relative risk (RR) was 0.93 and 95% confidence limits (CL) were between 0.64 and 1.36. Adjustment for a number of additional variables did not alter this estimate materially. Duration of OC use and interval since first use were similarly unrelated to the occurrence of melanoma. For women diagnosed before age 40, there was a crude positive association of 'ever' use of OC and melanoma (RR = 1.78; 95% CL, 1.11-2.86). However, adjustment for geography and other variables diminished this association and rendered it statistically not significant (RR = 1.43; 95% CL, 0.83-2.46). These data do not support the hypothesis that OC use is an independent risk factor for melanoma. (Author abstract) (24 Refs)

2. ORAL CONTRACEPTIVE USE AND ABORTION BEFORE FIRST TERM PREGNANCY IN RELATION TO BREAST CANCER RISK.

Vessey MP, McPherson K, Yeates D, Doll R
Dept. Community Medicine and General Practice, Radcliffe Infirmary, Oxford OX2 6HE, England
Br J Cancer; 45(3):327-331 1982

A recent publication from California in this journal has suggested that both prolonged oral contraceptive use and abortion before first term pregnancy increase the risk of breast cancer in young women. Data are presented on 1,176 women aged 16-50 yr with breast cancer, interviewed in London or in Oxford, together with a like number of matched control subjects. The results are entirely reassuring, being, in fact, more compatible with protective effects than the reverse. Possible reasons for the differences between the two sets of data are discussed. (Author abstract) (8 Refs)

ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER

3. PROMOTIVE EFFECTS OF STEROIDS AND BILE ACIDS ON HEPATOCARCINOGENESIS INITIATED BY DIETHYLNITROSAMINE.

Cameron RG, Imaida K, Tsuda H, Ito N
(c/o Ito) First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Cancer Res; 42(6):2426-2428 1982

The ability of four steroids and three bile acids to promote the appearance of hyperplastic foci and hyperplastic nodules initiated by diethylnitrosamine (DEN) in the liver of male Fischer rats was tested and compared with that of the known promoter phenobarbital (PB, 0.05%) as a standard value. Two weeks after a single dose of 200 mg of DEN per kg, the animals were exposed to test chemicals for 10 weeks. At 4 weeks following DEN, all treatment groups were subjected to partial hepatectomy. Of the steroids tested at the maximum tolerable doses, as determined in preliminary experiments, ethinyl estradiol was the most potent promoter, inducing more hyperplastic nodules than did PB and almost 50% less gamma-glutamyl transpeptidase-positive foci. However, gamma-glutamyl transpeptidase-positive foci induced by ethinyl estradiol were twice the average size as those induced by PB. The steroids testosterone, cortisone, and dexamethasone induced more foci than did DEN alone, but few if any hyperplastic nodules. Deoxycholic acid was the most potent promoter of the bile acids tested, inducing 3 to 4 times more hyperplastic nodules than did PB and more gamma-glutamyl transpeptidase-positive foci, which were 5 times larger on the average than those induced by PB. The other bile acids tested, lithocholic acid and taurine, induced slightly more foci than did DEN alone but no hyperplastic nodules. These findings suggest that ethinyl estradiol and deoxycholic acid are relatively strong promoters of the appearance of preneoplastic lesions in hepatocarcinogenesis. (Author abstract) (22 Refs)

4. RESEARCH ON THE MENOPAUSE.

WHO Scientific Group on Research on the Menopause, Bancroft J, Burger HG, Devi PK, Mack TM, Nordin BE, Nylander P, Ryan KJ, Sas M, Sinnathuray TA

World Health Organization, Geneva, Switzerland

WHO Tech Rep Ser (670): 120 pp., 1981.

The controversy over the existence of a menopausal syndrome of somatic and psychological symptoms and illness and the lack of data on the age distribution of menopause (MP) and on menopausal sociocultural significance in developing countries are discussed. The endocrinology of MP, age distribution, sociocultural significance of MP in different settings, symptoms associated with MP, disorders resulting from or possibly accelerated by MP, risks of therapeutic estrogens and progestins to peri- and postmenopausal women with particular reference to neoplasia, fertility-regulating methods for women approaching MP, and estrogens and the health care management of peri- and postmenopausal women are reported. Summaries of three studies of endometrial carcinoma conducted before 1975 and of case-control studies of endometrial cancer (EC) with epidemiological details are presented. Two major areas of ignorance in regard to risks of EC associated with estrogen therapy are the persistence of the oncogenic effect, and the nature of the dose-response curve at low doses and duration of use. Epidemiology of breast cancer (BC) is even more suggestive of endocrine origins than that of EC. Risk is related to a variety of endocrine phenomena, including ages at menarche, MP, and first pregnancy. Early oophorectomy has long been recognized to be strongly protective. Cohort studies and case-control studies of estrogen therapy and BC are presented. Several mechanisms for the relationship between endogenous hormones and BC have been proposed. Both naturally occurring and synthetic estrogens and progestins appear under some circumstances to be carcinogenic for BC in animal species. (383 Refs)

5. MAMMARY CANCER: HIGH RISK FACTORS FOR ITS DEVELOPMENT.

Torres Lobaton A, Diaz Perches R, Marquez GA, Miranda Hernandez H

Unidad de Oncologia, Hospital General de Mexico, S.S.A., Mexico, DF, Mexico

Rev Med Hosp Gen Mex; 44(8):281-287 1981

High risk factors in development of mammary cancer (MC) were discussed, and the following aspects were included: age, height, wt, heredity, dietary factors, personal history of MC, benign mammary pathology, exposure to ionizing irradiation, menstruation, menopause, parity, and hormones. Intake of estrogens under any form especially after menopause was also considered. (50 Refs) (In SPA)

MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES

6. BIOLOGICAL CHARACTERISTICS AND ESTROGEN AND PROGESTERONE RECEPTORS IN MAMMARY CARCINOMA INDUCED IN MALE SPRAGUE-DAWLEY RATS BY A SERIES OF INTRAGASTRIC INTUBATIONS OF 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Yoshida H, Yoshida A, Fukunishi R, Sato B, Okamoto S, Matsumoto K
Inst. Comparative Medicine and Animal Experimentation, Sch. Medicine, Ehime Univ., Shitsukawa, Shigenobu-cho, Onsen-gun, Ehime, 791-02, Japan
Cancer Res; 42(6):2434-2439 1982

Biological characteristics and estrogen (ER) and progesterone (PR) receptors were studied in male mammary carcinomas induced by 7,12-dimethylbenz(a)anthracene (DMBA) in male inbred Sprague-Dawley rats (MM). DMBA-induced carcinomas in females (MF) were used as controls. In 26 of 44 female rats given 20 mg DMBA once by gastric intubation at 50 days of age, MF with microscopic characteristics of cystic papillary adenocarcinoma developed 124 +-49 (S.D.) days after challenge. In all of the 42 male rats given 10 mg DMBA at 14-day intervals for 14 wk starting from 28 days of age, MM with microscopic characteristics of medullary adenocarcinoma developed 106 +-21 days after the first intubation of DMBA. The growth of primary MM was unaffected by orchiectomy or estrogen. Eighty to 100% of the MM transplanted in the four groups could grow in intact female rats, ovariectomized female rats, intact male rats, and castrated male rats, while the transplanted MF could grow only in intact female rats. The histology of MM was unchanged in primary and transplanted tumors under various hormonal conditions. ER were present in almost all of the hormone-independent primary and transplanted MM, although the levels for cytosol ER in MM were significantly lower than those in MF. Injection of 10 ug 17beta-estradiol induced marked synthesis of PR in primary and transplanted MM, even 24 and 48 hr after the 17beta-estradiol injection. These findings show that MM are hormone independent but, like hormone-dependent female tumors, contain ER and estrogen-dependent PR. (Author abstract) (24 Refs)

7. EFFECT OF CYTOTOXIC DRUGS ON ESTROGEN RECEPTOR LEVEL OF HUMAN BREAST CANCER CELLS (MCF-7) (MEETING ABSTRACT)

Yan KP, Samaan NA
University of Texas System Cancer Center, M. D. Anderson Hospital and, Tumor Institute Houston, TX, 77030
Proc Am Assoc Cancer Res; 23:940 1982

Effect of cytotoxic drugs on estrogen receptor (ER) content of human breast cancer was investigated on an extensively-used model for ER-positive human breast cancer, MCF-7 cell line. MCF-7 cells, growing in the log phase, were incubated in serum- and hormone-free medium with 10(-6)-10(-4) M methotrexate (MTX), 5-fluorouracil (5-FU), or vincristine (VCR) at 37 C for 3 hours. 3H-estradiol (3H-E2) was then added and the cells were incubated at 37 C for an additional hour. In addition to 3H-E2, duplicates received 200-fold excess radioinert diethylstilbestrol to determine nonspecifically bound 3H-E2. The intracellular specific binding of 3H-E2 to MCF-7 cells was measured by the method of Shafei and Brooks. Treatments of MCF-7 with MTX, 5-FU, or VCR resulted in a 25-64% reduction of 3H-E2 specific binding; and the reduction was dose-related. When MTX and 5-FU were administered in combination (1 x 10(-5) M each) to the cells, there was a synergistic decrease of ER level. Nuclear uptake of 3H-E2 in drug-treated MCF-7 was also significantly reduced (55-68% of control). Scatchard plot analysis reveals a reduction of receptor number with no change on binding affinity in the drug-treated cells. (1 Ref)

MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES

8. BENZO(A)PYRENE-INDUCED EARLY CYTOPATHOLOGIC CHANGES AND PEROXIDASE ACTIVITY IN THE ENDOMETRIUM OF OVARIECTOMIZED RATS.

Kang YH, Bui-Tran MT, West WL
Dept. Pharmacology, Coll. Medicine, Howard Univ., Washington, DC, 20059
Toxicol Appl Pharmacol; 63(2):242-256 1982

The compound benzo(a)pyrene (BP) (50 mg/kg/day sc once a day for 3-6 days) induced mitosis, peroxidase activity, and focal squamous cell metaplasia in the endometrial epithelium of ovariectomized rats. Diethylstilbestrol (DES) (20 ug/kg/day sc for 3-6 days) administered alone did not produce significant ultrastructural changes in the endometrial cells of castrated rats but did induce peroxidase activity. Concomitant administration of DES and BP induced significant cytopathological changes. Thus, BP alone can induce metaplasia in rat endometrium without the involvement of ovarian hormones, and DES may enhance the cytotoxicity of BP, apparently by stimulating uterine peroxidase activity that may be involved in the metabolic activation of BP. (33 Refs)

9. HUMAN PROLACTIN AND HUMAN GROWTH HORMONE ALTER CELL SHAPE AND PROLIFERATIVE RATE OF HUMAN BREAST CANCER CELLS IN CULTURE (MEETING ABSTRACT)

Shiu RP
Department of Physiology, University of Manitoba, Winnipeg, Manitoba R3E OW3, Canada
Proc Am Assoc Cancer Res; 23:933 1982

The role of prolactin and growth hormone in the etiology of human breast cancer is unclear. Therefore, the biological effects of these hormones on a human breast cancer cell line, T47D, were examined. T47D cells contain a high concentration of receptor sites that bind human prolactin(hPRL) and human growth hormone(hGH). When T47D cells were maintained on plastic substratum, they grew as a 'cobblestone' monolayer and assumed a flat, polygonal shape. However, when cultured in the presence of hPRL or hGH(10 ng/ml to 1 ug/ml), and 1 ug/ml each of hydrocortisone(H), insulin(I), and triiodothyronine(T3), T47D cells became round; the cells were loosely attached to the plastic substratum and they aggregated into large clusters. Such changes were not observed if only hPRL or hGH were present, or if only HIT3 were present, indicating that hPRL and hGH require the synergism of the other three hormones(HIT3) to induce the shape change in T47D cells. Another lactogenic hormone, ovine prolactin, produced a similar effect as hPRL and hGH, whereas non-lactogenic hormones such as ovine growth hormone and human luteinizing hormone had no effect on the T47D cells. As well as having an altered shape, T47D cells proliferated twice as fast in serum-free medium supplemented with HIT3 only; T47D cells failed to proliferate in serum-free medium not supplemented with hormones. (1 Ref)

10. LACK OF MUTAGENICITY BY NATURAL AND SYNTHETIC SEX HORMONES IN EPITHELIAL HUMAN CELLS (MEETING ABSTRACT)

Ferreri AM, Capucci A, Rocchi P, Prodi G

Institute di Cancerologia, Universita di Bologna, Bologna, Italy

VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

The mutagenic power of 17beta-estradiol and its synthetic analogous diethylstilbestrol was been tested in a human cell line (EUE). Five concentrations of both hormones were used (from 10-5M up to 10-10M) and cells were exposed to these compounds for 24 hrs. To assay the mutagenic action we used selection against diphtheria toxin, a protein synthesis inhibitor, in a dose of 0.05 Lf/ml; spontaneous stable mutants resistant to this drug are present in EUE cells at a frequency of 0-8x10(-6). The mutagenic power of each tested dose was assayed after expression times of 7 and 21 days: in all the experiments performed no mutagenicity by 17beta-estradiol and diethylstilbestrol was seen at any of the concentrations tested. These results may indicate that the compounds are not mutagenic, or that they are mutagenic but not detected as such by these experimental conditions. (1 Ref)

11. EFFECTS OF DIETARY PROTEIN ON RELEASE OF OVARIAN STEROIDS AND DEVELOPMENT OF DMBA-INDUCED BREAST TUMORS IN RATS (MEETING ABSTRACT)

Huang HH, Kissane JQ, Drab E, Hawrylewicz EJ

Department of Research, Mercy Hospital and Medical Center, Chicago, IL, 60616

Fed Proc; 41(3):280 1982

Virgin rats were fed 8%, 19.5% or 31% isocaloric protein diets for a period of 3 weeks before mating. The diets were maintained throughout the mating, gestation and lactation periods. After weaning, all pups were continued on their respective diets and ate ad libitum during the entire experimental period. DMBA (dimethylbenzanthracene) was administered intragastrically at dose of 3mg/100 g BW at the age of 3 weeks after vaginal opening. Serum estradiol and progesterone were measured at the time of DMBA administration and 6 months after DMBA treatment. Six months after DMBA 30% in 8%, 48% in 19.5%, and 73% in 31% protein diet rats exhibited breast tumors. Estradiol was significantly less in 8% protein group at 3 weeks after vaginal opening, as compared to the same stages of estrous cycle of 19.5% or 31% protein group; progesterone was significantly lower in 8% protein group at diestrous and proestrous afternoon as compared to those of high protein groups. There was no difference in estradiol and progesterone among these 3 groups of rats at 6 months after DMBA treatment. These data indicate that the lower incidence of DMBA-induced breast tumors in lower protein diets rats may be partly due to the low ovarian hormone profile at the time of DMBA exposure. (no Refs)

HORMONAL CARCINOGENESIS IN ANIMALS

12. THE PATHOGENESIS OF PLASMA CELL TUMORS.

Hollander VP, Platica M

Res. Inst., Hospital for Joint Diseases, New York, NY, 10035

The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

The possibility is examined that common factors are at play in the mineral-oil induced plasma cell tumors (PCT) in BALB/c mice because so many endocrine factors appear to modulate tumorigenesis. The working hypothesis involves bacterial lipopolysaccharide in a transformation step, pristane-induced peritoneal factors in the successful adaptation of nascent tumor cells to the host, and finally, an immunosuppression step which permits rapid growth. Hormones are involved in the earlier steps of plasmacytoma development. (145 Refs)

13. EFFECT OF ESTRADIOL PROPIONATE AND PREGNANCY ON CARCINOGENESIS INDUCED BY 1,2-DIMETHYLHYDRAZINE IN C3HA MICE.

Turusov VS, Murovannyi AN, Morozova OV

All-Union Cancer Res. Center, Moscow, USSR

Eksp Onkol; 4(2):20-23 1982

The effects of pregnancy and estradiol propionate (EP) administration on 1,2-dimethyl hydrazine (DMH)-induced carcinogenesis were studied in female C3HA mice. Virgin or pregnant females were subjected to sc administrations of DMH (8 mg/kg/wk) alone or in combination with EP (10 ug/kg/wk). DMH and EP were given for 30 wk. Animals were followed up for 50 wk after the initiation of the experiment. DMH alone induced tumors in 75% of virgin mice and in 56.2% of pregnant mice. EP administration resulted in a marked increase of the incidence of colonic tumors (31.6%, compared with 8.3% after administration of DMH alone to virgin mice and 18.7% after administration of DMH alone to pregnant mice). Uterine sarcomas were observed in 28.9% of mice treated with DMH + EP, while all mice treated with DMH alone were free of uterine sarcomas. Hepatocellular tumors were observed only in mice treated with DMH + EP (23.7%). These findings indicate that EP can modify the DMH-induced carcinogenesis not only in the hormone dependent organs but also in the liver and in the colon. (14 Refs) (In RUS)

REVIEWS AND OTHER RELATED STUDIES

14. THYROID ACTIVITY DURING HEPATOCARCINOGENESIS BY N-2-FLUORENYLACETAMIDE IN THE MALE RAT.

Aussel C, Lafaurie M, Castelli D, Formento JL, Stora C

Laboratoire d'Histologie et d'Immunologie, INSERM U210, 06034 Nice Cedex, France

Res Commun Chem Pathol Pharmacol; 36(1):105-117 1982

During chemical hepatocarcinogenesis by N-2-fluorenylacetamide, the hormonal status of male Sprague Dawley rats is modified. The histological study of the thyroid gland demonstrates a decreased activity evidenced by an augmentation of the follicle size and a reduced size of follicular epithelium. The level of T3 and T4 reflects in part this decreased activity.

Comparison with female rats treated in the same conditions shows an opposite effect of N-2-fluorenylacetamide. Indeed in the female, the thyroid gland presented an hyperactive state accompanied by a drastic decrease of serum T3 and T4. This difference in thyroid activity might take an important part in the mechanism responsible for the sex difference in liver cancer induction by N-2-fluorenylacetamide. (Author abstract) (19 Refs)

15. ESTROGEN EFFECTS ON RAT PITUITARIES WITH DIFFERENT TUMORIGENIC SUSCEPTIBILITY (MEETING ABSTRACT)

Eisenfeld AJ, MacLusky NJ, Visintin I
Yale University School of Medicine, New Haven, CT, 06520
Fed Proc; 41(3):1219 1982

With continuous high dose estrogen administration, it is well known that the pituitary of the Fischer 344 strain continuously grows to massive size while the pituitary of the Holtzman strain has little growth over the first few months. In the current study, Fischer and Holtzman rats received silastic implants of estradiol (E2). At 3 months the Fischer pituitary weighed 108+20 mg (ten times castrate) while the Holtzman pituitary averaged 33+3 mg (only twice castrate). Plasma E2 levels were in the same high range. As anticipated, cytosol E2 receptors were low in both strains. Using exchange conditions, the levels of E2 receptor in the nucleus per mg DNA were similar. Estrogen increased levels of cytosol progesterone receptor to the same extent. Utilizing the Sternberger technique for immunohistochemistry, more than half the cells contained prolactin. To study DNA synthesis, radioactive thymidine was injected 24 and 12 hours before pituitary removal. E2 markedly increased DNA synthesis; surprisingly, the percent of cells in S phase were identical in the two strains. The Fischer differed from the Holtzman in that a much higher percentage of the cells appeared abnormal (large nucleus, prominent nucleolus) by 3 months. The basis of the difference in pituitary growth and development of abnormal cells in response to estrogens requires further investigation. (no Refs)

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AUTHOR INDEX WITH CITATION NUMBERS

Aussel C	14
Bain C	1
Bancroft J	4
Belanger C	1
Bui-Tran MT	8
Burger HG	4
Cameron RG	3
Capucci A	10
Castelli D	14
Devi PK	4
Diaz Perches R	5
Doll R	2
Drab E	11
Eisenfeld AJ	15
Ferreri AM	10
Formento JL	14
Fukunishi R	6
Hawrylewicz EJ	11
Hennekens CH	1
Hollander VP	12
Huang HH	11
Imaida K	3
Ito N	3
Kang YH	8
Kissane JQ	11
Lafaurie M	14
MacLusky NJ	15
Mack TM	4
Marquez GA	5
Matsumoto K	6
McPherson K	2
Miranda Hernand	5
Morozova OV	13
Murovannyi AN	13
Nordin BE	4
Nylander P	4
Okamoto S	6
Platica M	12
Prodi G	10
Rocchi P	10
Rosner B	1
Ryan KJ	4
Samaan NA	7
Sas M	4
Sato B	6
Shiu RP	9
Sinnathuray TA	4
Speizer FE	1
Stora C	14
Torres Lobaton	5
Tsuda H	3
Turusov VS	13
Vessey MP	2
Visintin I	15
WHO Scientific	4
West WL	8
Willett W	1
Yan KP	7
Yeates D	2
Yoshida A	6
Yoshida H	6

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. MICROWAVE HEATING ENHANCES THE MIGRATION OF PLASTICIZERS OUT OF PLASTICS.
Bishop CS, Dye A
East Tennessee State Univ., Johnson City, TN, 37614
J Environ Health; 44(5):231-235 1982

2. DISEASES CAUSED BY EPOXY RESINS.
Konietzko H, Fischer O
Institut fur Arbeits- und Sozialmedizin, Johannes-Gutenberg-Universitat, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany
Zentralbl Arbeitsmed Arbeitsschutz Proph; 32(3):86-91 1982
In GER

3. NITROSAMINES.
Aigner K
Pneumonologische Abteilung, Krankenhaus der Elisabethinen, Fadingerstr. 1, A-4020 Linz-Donau, Austria
Wien Med Wochenschr; 132(71,Suppl):75-79 1982
In GER

4. EXPERIMENTAL TUMORS OF THE PERIPHERAL NERVOUS SYSTEM.
Beniashvili DS
Cancer Res. Center, Tbilisi, USSR
Eksp Onkol; 4(2):12-19 1982
In RUS

5. MUTAGENIC, CARCINOGENIC AND TERATOGENIC EFFECTS OF STYRENE.
Sram RJ, Pohlova H, Topinkova E
Klinika hygieny a epidemiologie, Srobarova 48, 100 42 Prague 10, Czechoslovakia
Prac Lek; 34(2):68-72 1982
In CZE

6. DIETHYLSTILBESTROL: EFFECT OF IN UTERO EXPOSURE.
Burke L
Obstetrics/Gynecology Dept., Harvard Medical Sch., Boston, MA
Curr Probl Obstet Gynecol; 5(2):1-58 1981

7. IN UTERO EXPOSURE TO DIETHYLSTILBESTROL: ADVERSE EFFECTS ON THE REPRODUCTIVE TRACT AND REPRODUCTIVE PERFORMANCE IN MALE AND FEMALE OFFSPRING.
Stillman RJ
Dept. Obstetrics and Gynecology, George Washington Univ. Sch. Medicine and Health Sciences, 2150 Pennsylvania Ave., NW, Washington, DC, 20037
Am J Obstet Gynecol; 142(7):905-921 1982

8. BIOLOGICAL EFFECTS OF MINERAL WOOL.
Petersen R, Ehrhorn H, Mousing K, Sabroe S, Silberschmid M, Venstrup-Nielsen SE
Socialmedicinsk institut, Vesterbro Torv 1-3, DK-8000 Arhus C, Denmark
Ugeskr Laeger; 144(13):971-975 1982
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9. NATURALLY OCCURRING FOOD TOXICANTS: PHENOLIC SUBSTANCES OF PLANT ORIGIN COMMON IN FOODS.
Singleton VL
Dept. Viticulture and Enology, Univ. California, Davis, CA
Adv Food Res; 27:149-242 1981

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Sugimura T
Natl. Cancer Res. Inst., Tsukiji, Chuo-ku, Tokyo, Japan
Cancer; 49(10):1970-1984 1982

11. THE BIOLOGICAL EFFECTS OF CARRAGEENAN AND OTHER SULFATED POLYSACCHARIDES WITH PARTICULAR ATTENTION TO IMMUNOLOGICAL AND CARCINOGENIC PROPERTIES.
Larsen B
Kraeftforskningsinstituttet, DK-8000 Arhus C, Denmark
Ugeskr Laeger; 144(12):860-863 1982
In DAN

12. VARIATIONS AMONG SPECIES AND CELL TYPES IN THE EFFECTS OF CAFFEINE ON MUTAGEN-INDUCED CYTOTOXICITY AND POSTREPLICATION REPAIR OF DNA.
Sivak A, Rudenko L, Teague LG
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EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

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15. STUDIES OF CANCER EPIDEMIOLOGY IN THE UNITED STATES OF AMERICA.
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16. CURRENT CONCEPTS OF THE ETIOLOGY AND PATHOGENESIS OF LUNG CANCER.
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Psychosomatics; 22(9):774-793 1981

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Dept. Environmental Health, Univ. Washington, Seattle, WA, 98195
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Neiman IM
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ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

21. POLYCHLORINATED BIPHENYLS (PCBS): AN AUSTRALIAN VIEWPOINT ON A GLOBAL PROBLEM.
Richardson BJ, Waid JS
Marine Science Lab., Ministry for Conservation - Victoria, P.O. Box 114, Queenscliff, Victoria 3225, Australia
Search; 13(1/2):17-25 1982

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Onkologiska kliniken, Lasarettet, Lund, Sweden
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Lakartidningen; 79(15):1457-1459 1982
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CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

24. REGULATION OF GENE EXPRESSION IN NORMAL AND NEOPLASTIC CELLS. A REVIEW.
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Pathobiol Annu; 11:1-29 1981

25. WHAT ARE ISOZYMES TELLING US ABOUT GENE REGULATION IN CANCER?
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Fels Res. Inst., Temple Univ. Sch. Medicine, Health Sciences Center, Philadelphia, PA, 19140
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26. CHANGES IN AMINO ACID AND SUGAR TRANSPORT ACTIVITY ASSOCIATED WITH MALIGNANT TRANSFORMATION.
Nishino H, Inui K
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Arkh Patol; 44(2):69-73 1982
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Dept. Veterinary Science, Coll. Agricultural and Life Sciences, Univ. Wisconsin, 1655 Linden Drive, Madison, WI, 53706
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Groopman JE, Gottlieb MS
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Hosp Pract; 17(5):64F-64G,64J,64N,64O,64R,64T 1982

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37. MAJOR APPROACHES TO THE EXPERIMENTAL STUDY OF LUNG CANCER.
Pliss GB, Turusov VS, Zabezhinskii MA
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Zaklad Genetyki Czlowieka, PAN, 60-479 Poznan, Poland
Pol Tyg Lek; 37(2):63-67 1982
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39. CANCER - PRINCIPLES AND PRACTICE OF ONCOLOGY.
DeVita VT, Hellman S, Rosenberg SA

NCI, Bethesda, MD
Cancer - Principles and Practice of Oncology. Philadelphia, Lippincott, 1926 pp., 1982

40. MOVABLE GENETIC ELEMENTS

Watson JD
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Cold Spring Harbor Symp Quant Biol 45(part 1): 445 pp., 1981.

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OCTOBER, 1982

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In this issue:

- **ORAL CONTRACEPTIVES AND HUMAN CANCER** 1-4
- **ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER** 5-11
- **MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES** 12-13
- **MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES** 14
- **HORMONAL CARCINOGENESIS IN ANIMALS** 15-19
- **REVIEWS AND OTHER RELATED STUDIES** 20-34

ORAL CONTRACEPTIVES AND HUMAN CANCER

1. ORAL CONTRACEPTIVES AND PROLACTINOMAS: A CASE-CONTROL STUDY.

Maheux R, Jenicek M, Cleroux R, Beauregard H, De Muylder X, Gratton NM, Van Campenhout J
Centre d'infertilite et d'endocrinologie de la reproduction, Hopital Saint-Francois d'Assise, 10, rue de l'Espinay, Quebec, P.Q. G1L 3L5, Canada
Am J Obstet Gynecol; 143(2):134-138 1982

The increase in the number of newly diagnosed cases of prolactinomas seems to coincide with the use of oral contraceptives during the past 2 decades. The following retrospective case-control study was undertaken in an attempt to disprove a null hypothesis of relationship between oral contraceptive use and prolactinomas. Each of 70 patients operated upon for removal of a prolactinoma was closely matched for age, gravidity, and year of final diagnosis with one patient in each of three control groups. The control groups selected were constituted, respectively, of patients with secondary amenorrhea and normal prolactin levels, patients with normal ovulatory cycles consulting for infertility, and subjects without medical or gyne-

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cologic problems. No statistically significant differences were found in the exposure rates to oral contraceptives among the four groups. This study thus failed to reveal a significant association between prolactinomas and oral contraceptives but, given the sample size, a relative risk lower than 3.32 cannot be demonstrated or disproved. (Author abstract) (23 Refs)

2. RISK FACTORS FOR BREAST CANCER IN WOMEN IN NORTHERN ALBERTA, CANADA, AS RELATED TO AGE AT DIAGNOSIS.

Lubin JH, Burns PE, Blot WJ, Lees AW, May C, Morris LE, Fraumeni JF

Environmental Epidemiology Branch, Div. Cancer Cause and Prevention, NCI, NIH, Public Health Service, U.S. Dept. Health and Human Services, Bethesda, MD, 20205

JNCI; 68(2):211-217 1982

A population-based case-control study involving interviews with 577 female breast cancer patients and 826 controls in northern Alberta, Canada, revealed that some determinants of breast cancer varied according to age. Among women under age 45, risk factors included a younger age at menarche, late age at last birth, high parity, and recent use of oral contraceptives. At older ages risk was related to natural as opposed to surgical menopause, late age at first birth, low parity, late age at natural menopause, and tonsillectomy. At all ages there was an increased risk of breast cancer associated with difficulty in conceiving, benign breast disease, not having breast fed, and a history of breast cancer among mothers or sisters. For some variables the age differences were pronounced; the combination of low parity and late age at first birth was associated with a sevenfold increase in breast cancer risk at ages 55-80 but a slight decrease at ages under 45. The effect of tonsillectomy steadily increased with age and represents a new lead, but certain features of the data suggest that the link to oral contraceptives among younger women and the inverse relation to breast feeding at all ages may not be causal. Even though design limitations (cases interviewed in a different setting from controls) appeared not to influence conclusions, the results may have been subjected to interview bias and thus should be interpreted cautiously. (Author abstract) (26 Refs)

3. EPITHELIAL OVARIAN CANCER AND COMBINATION ORAL CONTRACEPTIVES.

Rosenberg L, Shapiro S, Slone D, Kaufman DW, Helmrich SP, Miettinen OS, Stolley PD, Rosenshein NB, Schottenfeld D, Engle RL

Drug Epidemiology Unit, Boston Univ. Sch. Medicine, 777 Concord Ave., Cambridge, MA, 02138

JAMA; 247(23):3210-3212 1982

The risk of epithelial ovarian cancer in relation to the use of combination oral contraceptives was evaluated in a case-control study of women younger than 60 yr. Combination oral contraceptives were used by 35 (26%) of 136 cases and 187 (35%) of 539 controls. The relative risk estimate for combination oral contraceptive use was 0.6 (95% confidence interval, 0.4 to 0.9). The reduction in risk appeared to persist for as long as 10 years after use had ceased and to be greater for longer durations of use, but these results were not statistically significant. The findings were not explained by parity or by other identified potential confounding factors. The results suggest that the use of combination oral contraceptives protects against epithelial ovarian cancer. (Author abstract) (16 Refs)

4. OCCURRENCE AND HISTOLOGICAL STRUCTURE OF ADENOCARCINOMA OF THE ENDOCERVIX AFTER LONG-TERM USE OF ORAL CONTRACEPTIVES.

Dallenbach-Hellweg G

Frauenklinik im Klinikum Mannheim, Univ. Heidelberg, Theodor-Kutzer-Ufer, 6800 Mannheim 1, W. Germany

Geburtshilfe Frauenheilkd; 42(4):249-255 1982

In the last 10 yr we have studied 21 adenocarcinomas of the endocervix developing in women up to the age of 50. Sixteen of these women had taken oral contraceptives, in most instances continuously for 1 to 16 yr, on the av for 10 yr. During the same period of time we collected eight adenocarcinomas in situ of the endocervical mucosa, seven of which developed after 1 to 20 yr of use of oral contraceptives. Ten of the 16 patients with adenocarcinomas and 5 of those with adenocarcinomas in situ had taken oral contraceptives containing norgestrel as gestagen. The others had taken either norethisterone acetate or lynestrol. Histologically 8 of the 16 carcinomas were well-differentiated, 5 were mucoepidermoid and 3 microalveolar adenocarcinomas. In two of the five patients who had not taken oral contraceptives, the adenocarcinomas were well-differentiated, the remaining three were poorly differentiated but without mucoepidermoid qualities. In the women taking the oral contraceptives an adenomatous hyperplasia of the endocervix developed either prior to or at the same time as the adenocarcinoma. Eight of 10 rhesus monkeys (NCI) treated every 84-90 days for 10 yr with medroxyprogesterone acetate at doses 50x those prescribed for women developed the same types of adenocarcinomas. These studies strongly suggest that the use of gestagens for many yr is causally related to the development of these generally rare adenocarcinomas. These results warrant further investigations. (Author abstract) (29 Refs) (In GER)

ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER

5. THE ROLE OF ESTROGENS IN MASTOPATHY AND MAMMARY CANCER IN PERIMENOPAUSAL WOMEN.

Greenblatt RB, Vasquez J, Samaras C, Nezhat C

Dept. Endocrinology, Medical Coll. Georgia, Augusta, GA, 30901

J Am Geriatr Soc; 30(3):165-169 1982

Fibrocystic disease of the breast (FCD) is an exaggeration of the normal physiologic response to cyclic estrogen and progesterone stimulation. The disorder can persist, with much less severity, in the menopausal woman. Whether FCD predisposes to mammary cancer remains moot. A new steroidal agent, danazol, can eliminate nodosities in the majority of women with FCD. Thermography may identify women who are at greater risk because of increased heat production. Mammography should be employed in women with persistently abnormal thermograms, even though no suggestive breast masses are palpable. Needle biopsy or surgical biopsy should be undertaken whenever a firm indurated mass is palpated, regardless of negative findings with a thermogram or mammogram. In a series of 1,548 women treated for 10,715 women-years, the incidence of breast cancer after prolonged estrogen therapy was not increased. Although estrogens and prolactin have been incriminated in the etiology of mammary cancer, no hard facts exist to confirm such allegations. (Author abstract) (34 Refs)

6. METABOLIC EPIDEMIOLOGY OF LARGE BOWEL CANCER.

Hill MJ
Central Public Health Lab., Colindale Ave., London NW9, England
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

The epidemiology of large bowel cancer and predisposing and associated diseases are reviewed. Possible causative agents, evidence for the role of bile acids as co-carcinogens, and metabolic epidemiology vis results of studies of the histopathology of large bowel cancer and the adenoma-carcinoma sequence are considered. Variables examined in relation to the development of large bowel cancer include geography, sex, socioeconomic group, race, religion, population density, time and cultural environment. Predisposing diseases include adenomatosis coli, cancer family syndrome, and colorectal adenoma. Associated diseases include associated cancers, diseases of fiber depletion, and others. Possible causative agents are stress and physical factors, radiation, immunological factors, virological factors, environmental agents, endogenous agents (cholesterol, bile acids, steroid estrogens, tryptophan metabolites, tyrosine metabolism, and N-nitroso compounds), nutrition, and genetic factors. (154 Refs)

7. FURTHER STUDIES ON SKIN MELANOMAS APPARENTLY DEPENDENT ON FEMALE SEX HORMONES.

Lee JA, Storer BE
Sch. Public Health and Community Medicine, Dept. Epidemiology SC 36, Univ. Washington, Seattle, WA, 98195
Int J Epidemiol; 11(2):127-131 1982

In the British Isles the incidences and mortality rates from malignant melanoma of the skin have been shown to be higher in females than in males in the later years of reproductive life. In populations with higher rates for malignant melanoma of skin (Scandinavia, Australasia, etc), and also in Japan, where the rates are low, the ratio of female to male deaths is lower than in the British Isles. However, a similar pattern of age-specific sex ratios (risks for females compared with males peaking at some age in the latter half of reproductive life, and relatively low in middle age) is found in these populations. This 'gynecologic' factor is not an artifact of interactions between age and year of birth effects, and appears to act multiplicatively with other etiologic factors. These findings have implications for studies of the etiology and pathogenesis of malignant melanoma, as well as for the descriptive mathematical modelling of the rates for purposes of environmental legislation. (Author abstract) (22 Refs)

8. BREAST CANCER 4: ADVANCES IN RESEARCH AND TREATMENT.

McGuire WL
Div. Oncology, Dept. Medicine, Univ. Texas Health Science Center, San Antonio, TX, 78284
Breast Cancer 4: Advances in Research and Treatment. New York, Plenum Medical Book Company, 234 pp., 1981.

Breast cancer studies examining a variety of questions are reviewed. Topics include methods to predict response to chemotherapy, both in vivo and in vitro; estrogen receptors as a prognostic indicator, from theoretical and clinical points of view; histopathology and hormone dependence of benign breast disease, its relationship to breast cancer, and the role of exogenous estrogens in incidence; a patient's review of the progress in biology, etiology and epidemiology, detection and diagnosis, primary treatment, adjuvant therapy, metastatic disease, and psychosocial aspects of breast cancer between 1970 and 1980; the history, development, and prospects for breast cancer detection center projects; reconstruction of the female breast after mastectomy, including initial interview, alternatives in reconstructive surgery, chemotherapy, selection of appropriate patients, follow-up, and concern for the other breast; the woman at high risk for breast cancer and the use of prophylactic mastectomy; and comparative study of histological characteristics and 10-yr survival rates between Japanese and American breast cancer patients. (493 Refs)

9. SQUAMOUS METASTASES FROM PROSTATIC ADENOCARCINOMA (MEETING ABSTRACT)

Accetta PA, Gardner WA
Department of Pathology, Vanderbilt University School of Medicine, Nashville, TN
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

The propensity for prostatic glandular and ductal epithelium to undergo squamous metaplasia in response to infarction and estrogen is well known. Squamous change within malignant epithelium is much less common, and only three cases in the world literature report malignant squamous change in metastases of adenocarcinoma of the prostate. Recently, we discovered two patients with widespread metastatic adenocarcinoma of the prostate who exhibited at autopsy squamous metastases of such extent and distribution that a second primary neoplasm was sought. In neither case was another primary found after complete autopsy. Furthermore, immunoperoxidase staining for prostatic acid phosphatase (PAP) was positive in foci of adenocarcinoma as well as in transition areas where the glandular epithelium merged with squamous carcinoma. In one case, even individual squamous cells were PAP-positive. Since no foci of malignant squamous epithelium were seen in residual prostate tissue at autopsy, we believe the squamous change in the metastases represented a local metaplastic phenomenon rather than automonous spread of a malignant squamous component. As with the three previously reported cases, both patients had received long-term estrogen treatment. Furthermore, both cases demonstrated alterations of the type usually associated with estrogen therapy. Such changes were not seen in pretreatment biopsy specimens. It therefore seems likely that the squamous metastases in these cases were related to long-term DES (diethylstilbestrol) therapy. This phenomenon should be considered when an otherwise obvious metastatic squamous carcinoma occurs in a patient being thus treated. (no Refs)

10. THE DESMOID TUMOR. II. ANALYSIS OF FACTORS POSSIBLY CONTRIBUTING TO THE ETIOLOGY AND GROWTH BEHAVIOR.

Hayry P, Reitamo JJ, Totterman S, Hopfner-Hallikainen D, Sivula A
Transplantation Lab., Univ. Helsinki, Haartmaninkatu 3, SF 00290 Helsinki 29, Finland
Am J Clin Pathol; 77(6):674-680 1982

Eighty histologically verified cases of the desmoid tumor (DT) have been analyzed with regard to factors possibly contributing to the etiology and/or growth behavior of this uncommon neoplasm. Considering the four statistical age components, the 'fertile' female and 'menopausal' varieties of the DT grew distinctly faster (0.1 less than p greater than 0.05 and less than 0.05), and the female 'juvenile' variety distinctly slower (0.1 less than p greater than 0.05) than the male DTs. In a visual estimate, the fertile female patients had a significant (p less than 0.01) predisposition to estrogen predominance, while fewer patients than expected displayed progesterone predominance or were at balance (p = NS and less than 0.01, respectively). Thirty-two percent of the patients with an abdominal DT had previously operated in the region of subsequent tumor growth. Significantly more pregnancies were observed in patients with abdominal DT than with extra-abdominal DT (p less than 0.05). On only one occasion did sigmoideoscopy reveal colonic polyposis (Gardner's syndrome). The most striking observation was, however, that up to 80% of the affected patients (compared with less than 5% in the normal control population, p less than 0.05) had multiple minor bone anomalies demonstrable by x-ray screening of the mandible, chest, and long bones. We suggest that a generalized (inherited or mutant) defect in growth regulation of connective tissue is the most important underlying cause for the DT. However, the other factors, including hormonal effects, trauma and pregnancy contribute to the growth behavior of the tumor. (Author abstract) (13 Refs)

11. OESTROGENS AND OBESITY AS RISK FACTORS FOR ENDOMETRIAL CANCER IN ITALY.

La Vecchia C, Franceschi S, Gallus G, Decarli A, Colombo E, Mangioni C, Tognoni G
Istutito di Richerche Farmacologische 'Mario Negri', Via Eritrea, 62-20157 Milano, Italy
Int J Epidemiol; 11(2):120-126 1982

In a case-control study to evaluate risk factors for endometrial cancer, obesity, history of various diseases, reproductive and menstrual characteristics, marital status, education, and lifetime use of female hormones were examined in 173 histologically proven endometrial cancers and 347 controls. Obesity, non-contraceptive estrogen use, late menopause, low parity and history of uterine fibromyomas were associated with an increased risk of endometrial cancer. The relative risks of obesity and estrogen use seem to fit well for an additive model. Histological differentiation was positively correlated both to estrogen use and to level of overweight, supporting the hypothesis of a specific role of estrogens in endometrial cancer. (Author abstract) (21 Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES

12. DECREASED NOCTURNAL PLASMA MELATONIN PEAK IN PATIENTS WITH ESTROGEN RECEPTOR POSITIVE BREAST CANCER.

Tamarkin L, Danforth D, Lichter A, DeMoss E, Cohen M, Chabner B, Lippman M
NIH, Building 6, Room 136, Bethesda, MD, 20205
Science; 216(4549):1003-1005 1982

Plasma melatonin concentrations were determined over a period of 24 hr in 20 women with clinical Stage I or II breast cancer. In 10 of the patients, whose tumors were estrogen receptor positive, the nocturnal increase in plasma melatonin was much lower than that observed in 8 control subjects. Women with the lowest peak concentration of melatonin had tumors with the highest concentrations of estrogen receptors. A significant correlation was found between the peak plasma melatonin concentration and the tumor estrogen receptor concentration in 19 of the patients. These data suggest that low nocturnal melatonin concentrations may indicate the presence of estrogen receptor positive breast cancer and could conceivably have etiologic significance. (Author abstract) (18 Refs)

13. NUCLEAR ESTROGEN BINDING IN HORMONALLY AND NON-HORMONALLY INDUCED RENAL CARCINOMA (MEETING ABSTRACT)

Sufrin G, Alvarez J, Swaneck G
No affiliation given
77th Annual Meeting of the American Urological Association, Inc; May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Animal models of Renal Carcinoma (RC) have been described and the estrogen induced RC of the hamster is a unique example of a hormonally induced and hormonally dependent neoplasm. Since a critical requirement of estrogen responsive tissue is estrogen binding to their nuclei, we studied nuclear estrogen binding in this tumor and in RC induced in rats by the non-hormonal drug streptozotocin. RC was obtained from male hamsters after continuous (8-10 months) treatment with diethylstilbestrol (DES) (total dose, 300mg) and from male Wistar Furth rats 9-11 months following a single injection of streptozotocin (65 mg/kg). Purified renal nuclei were isolated and nuclear estrogen binding measured using a tritiated estradiol (3HE2, 98Ci/mmol) exchange assay. Specific binding was determined by subtracting total from non-specific binding. Saturation analysis of hamsters RC nulcei showed a 6-10 fold increase in the amount of 3HE2 specifically bound as compared to nuclei from untreated animals. In contrast, no increase 3HE2 binding was observed when abdominal muscle nuclei or liver nuclei from DES treated animals were compared to muscle or liver nuclei from untreated controls. The amount of 3HE2 bound by nuclei from streptozotocin induced RC showed no change as compared to untreated controls. Moreover when renal nuclei from Wistar Furth rats who were treated with DES for 8 months and who do not develop RC in response to chronic DES were compared to untreated controls, no change in 3HE2 binding was noted. The estrogen induced and estrogen dependent hamster RC exhibits binding characteristics associated with estrogen target tissue and with other estrogen dependent tumors. (no Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES

14. SELENIUM, ESTRADIOL 17BETA, NITRITES, AND HUMAN BREAST CANCER.

Lombard LF
11145 Northborough Lane, Richmond, VA, 23235
Med Hypotheses; 8(4):371-382 1982

An hypothesis postulating an etiology of breast cancer from interactions among selenium, estradiol 17beta, nitrites, and RBC is presented. In this hypothesis, in the presence of nitrites, triglycerides, and selenium, estradiol 17beta is catalyzed by an unknown enzyme (' X') to form the known carcinogen chrysene, which is complexed with methemoglobin in the RBC. The conversion process may partially take place in the gastrointestinal tract and liver, with more direct conversion in breast cells after transport. Chrysene, in the breast cells, already under attack by nitrites or lysosomal enzymes, causes additional focal hyperplasia, metaplasia, neoplasia, anaplasia, gene alteration, and carcinoma. The process may also require high androgen levels and other trace elements, such as zinc. (51 Refs)

HORMONAL CARCINOGENESIS IN ANIMALS

15. DIETHYLSTILBESTEROL INDEPENDENT GROWTH OF ESTROGEN INDUCED/DEPENDENT RENAL ADENOCARCINOMA CELLS IN CULTURE (MEETING ABSTRACT)

Naylor PH, Loring JM, Villee CA
Department of Biological Chemistry, Harvard Medical School, Boston, MA
148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C. American Association for the Advancement of Science 182 pp., 1982.

Understanding the mechanism of hormone induced and/or dependent tumor growth is critical to both prevention and control of many neoplasms. Both estradiol and diethylstilbesterol (DES) at pharmacological concentrations in serum induce renal adenocarcinoma in the Syrian hamster. Since primary tumors require DES for growth when transplanted, we have been studying renal carcinomas in primary culture to define the requirements for tumor growth. Cell growth is assessed both by the numbers of cells 6 days' post culture and by DNA synthetic activity as measured by radiolabeled thymidine incorporation at days 3 and 6 post culture. Fatal calf serum (10%) added to minimal essential media increases cell growth and DNA synthesis compared to 10% calf serum supplemented media. DES does not constantly increase either cell growth or DNA synthesis under any conditions tested. These results are interpreted as being consistent with our developing hypothesis that DES is acting indirectly (most probably via a pituitary product) rather than directly affecting tumor cell growth. (no Refs)

16. EFFECTS OF MEDROXYPROGESTERONE ACETATE ON THE DEVELOPMENT OF DIMETHYLBENZANTHRACENE-INDUCED MAMMARY TUMORS. POSSIBLE MODES OF ACTION (MEETING ABSTRACT)

Danguy A, Legros N, Leclerq G, Heuson JC
Laboratory of Histology and Laboratory of Mammary Oncology, Brussels, Belgium
International Symposium on Medroxyprogesterone Acetate, February 24-26, 1982, Geneva, Switzerland. Farmatalia Carlo Erba 91 pp., 1982.

Our purpose was to describe the effects of different doses of Medroxyprogesterone acetate (MPA) on growth of 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors and to study the underlying endocrine mechanisms. This experimental model is extensively studied in order to understand the hormonal dependency of human breast cancer. MPA was administered sc at doses of 1 mg/kg, 10 mg/kg and 100 mg/kg 6 days a week for 6 weeks. The smaller dose enhanced tumor growth whereas the higher one was significantly inhibitory. The administration of 100 mg/kg/day of the drug to ovariectomized rats significantly inhibited the increase in body weight as compared to ovariectomy alone. In the animals treated with 10 and 100 mg/kg/day the ovaries contained very small follicles and no corpora lutea; the adrenals were also distinctly small with atrophy of the cortical components. Using sensitive histological (Peroxidase anti-Peroxidase Complex unlabelled antibody stain, immunofluorescence) and endocrine (Radioimmunoassay) techniques we were able to demonstrate the modifications produced by MPA in the pituitary gland and the serum: atrophy of adenocorticotropes, gonadotropes and mammotropes as well as decrease in plasma Luteinizing Hormone (LH) and Prolactin (PRL). So the antitumor activity of MPA may be explained by a partial pharmacological hypophysectomy. However it remains possible that part of the inhibitory action of MPA may be exerted directly at the tumor level. Indeed, the action of MPA via the progesterone receptor and a direct cytotoxic effect of the drug must be drawn into consideration. (no Refs)

17. INFLUENCE OF DAILY SUBCUTANEOUS ADMINISTRATION OF 6-METHYLPREDNISOLONE AND ORAL APPLICATION OF 30% SALINE SOLUTION ON TUMORIGENESIS INDUCED IN MOUSE STOMACH BY SINGLE APPLICATION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Wagner G, Habs M, Schmahl D
(c/o Habs) Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
J Cancer Res Clin Oncol; 103(2):207-209 1982

Low-dose dimethylbenz(a)anthracene (25 mg/kg po by gavage on day 1) produced papillomas in the forestomach of female C57BL/6 mice treated with 6-methylprednisolone (MP: 80 mg/kg/day sc on days 1-3) and 30% NaCl (0.25 ml/animal, days 1-3, 1 hr after MP, by gavage). Hyperplasia/hyperkeratosis was observed in 5/20 animals and papilloma in 12/20 animals. Median latent period for papilloma development was 25 days. The results indicate that in an altered environment small amounts of a chemical carcinogen suffice to induce tumors. (7 Refs)

18. ANDROGEN REGULATION OF DMN-N-DEMETHYLASE ACTIVITY IN KIDNEY OF BALB/C MICE (MEETING ABSTRACT)

Mohla S, Ahir S, Ampy FR
Department of Oncology, Howard University College of Medicine, Washington, DC, 20060
Med Pediatr Oncol; 10(1):102 1982

Androgenic hormones have been shown to regulate the biotransformation of Dimethylnitrosamine (DMN) to its active mutagenic metabolite. This androgenic regulation in renal tissue is a receptor mediated phenomenon as androgens are not able to stimulate kidney microsomal enzymes required for Ames test, in Tfm mice. Further, even though hepatic emzymes are more active than the kidney enzymes, the androgen effect is tissue (kidney) specific. Recent observation indicates that this androgenic effect is observed only under conditions when androgen receptors are translocated in the nucleus. The present experiments were designed to test correlations between the mutagenic ability of renal tissue and its N-demethylase activity (an enzyme implicated in conversion of DMN to its active metabolite). N-demethylase activity was measured from micromosomal fractions of liver and kidney (by quantitating formaldehyde formation) according to Nash. The results indicate: (1) higher DMN-N-demethylase activity in liver (male or female, adults) compared to kidney (male or female); (2) higher enzyme activity in adult male compared to adult female renal tissue; (3) complete loss of renal but not liver enzyme activity in mice castrated for 7 days (testosterone treatment, 2 mg/day/10 days, can significantly increase enzyme activity of kidney tissues in such castrates); and (4) a significant increase in DMN-N-demethylase activity in renal tissue of testosterone treated adult female mice. These data indicate androgenic regulation in kidney DMN-N-demethylase activity. The BALB/c mouse kidney system is a useful model to study the mechanism(s) by which steroid hormones augment or inhibit biotransformation of procarcinogens to mutagens which may ultimately lead to tumorigenesis. (2 Refs)

19. LOCALIZATION OF ALPHA-MELANOCYTE-STIMULATING HORMONE IN THE PITUITARY OF NORMAL HAMSTERS AND IN ESTROGEN-INDUCED PITUITARY TUMORS (MEETING ABSTRACT)

Finkelstein JA, Lee IM, Lotstra F, Steggles AW, Vanderhaeghen JJ
Northeastern Ohio Universities College of Medicine, Rootstown, OH
Anat Rec; 202(3):57A 1982

Immunocytochemistry was used to localize alpha-melanocyte-stimulating-hormone-like immunoreactivity (alpha-MSH) in the pituitary gland of normal hamsters and of hamsters with estrogen-induced pituitary tumors. The tumors were induced by subcutaneous implantation of diethylstilbestrol (DES). After nine months of treatment, experimental animals and age-matched controls were sacrificed. Pituitaries were fixed by immersion in Bouin's, embedded in paraffin and processed by the indirect peroxidase-anti-peroxidase technique, using an antibody to alpha-MSH. In the normal pituitary, alpha-MSH-containing cells formed a band between the neural lobe and the pituitary cleft and were completely co-extensive with the intermediate lobe. A few immunoreactive cells were seen in the anterior lobe either immediately adjacent to the intermediate lobe or scattered randomly. Treatment with DES produced enlarged pituitaries; sometimes it was difficult to distinguish clearly the three separate lobes of the pituitary. In other experimental animals in which the three lobes were definable, the enlargement was due to increased size of both the anterior and intermediate lobes, with a consequent compression of the posterior lobe. One effect of DES treatment in the intermediate lobe, was an increase in the number of alpha-MSH-containing cells which showed different intensities of staining; densely stained cells tended to be prominently organized around lumina. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

20. CANCER: A COMPREHENSIVE TREATISE. VOLUME 1. ETIOLOGY: CHEMICAL AND PHYSICAL CARCINOGENESIS. SECOND EDITION.

Becker FF
Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer: A Comprehensive Treatise. Volume 1. Etiology: Chemical and Physical Carcinogenesis. Second Edition. New York, Plenum Press, 714 pp., 1982.

In order to eradicate cancer, carcinogenic agents must be identified and their mechanism of action, understood. Crucial interactions between these carcinogens and important macromolecules within the cell must be identified, and those which relate to carcinogenesis must be distinguished from those which are extraneous. The alterations of cell function induced by these reactions must be examined so that phenotypic variation may be understood and an explantation provided for why malignant cells escape from normal homeostatic control. Malignancy must be defined so that the characteristics of cellular activity that permit the malignant cell to compete so effectively with the normal constituent can be defined. The goals of cancer research in general and of the present text are reflected in chapters on cytogenetics, hormones, immunocompetence, chemical carcinogenesis, metabolism of chemical carcinogens, interactions of carcinogens with nucleic acids, effects of carcinogens on cell organelles, sequential aspects and effects in chemical carcinogenesis, radiation, radiation carcinogenesis, and cancer associated with asbestosis, schistosomiasis, foreign bodies, and scars. (3320 Refs)

21. GENETICS: ANIMAL TUMORS.

Heston WE
Lab. Biology, NCI, NIH, Bethesda, MD
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Genetics has helped determine that cancer is not a single disease but a group of different diseases. Genetics has helped integrate the approaches to cancer research for each approach has had to take into account genetic elements. Same form of tumor occurs in the most lowly multicellular organism with little normal cell differentiation, which indicates that the basic neoplastic change involves a very primitive physiological process. Tumors have been studied extensively in invertebrates such as the diploblastic coelenterates and insects. There is evidence among the vertebrates that in the evolution of the species certain gene complexes have been sorted out to give rise to specific tumors in certain species. Tumors have been studied in fish, fowl, birds, and mammals, particularly the rat and mouse. Selectivity of the species has been demonstrated through hybridization studies which indicate that cancer is a negative selective factor in the evolution of species. Inbreeding has been used in cancer research to provide high tumor strains of animals. Other topics reviewed are the genetics of spontaneous tumors, of chemically induced tumors, of hormonally induced tumors, and of virally-induced tumors. (90 Refs)

22. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.

Furth J
Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Hormones as etiological agents in neoplasia are discussed. The basic properties of human hormones are reviewed, and general considerations in the detection of hormonal activity are listed. Brief general comments are presented on tumors in peripheral areas illustrating the diversity of pathogenic mechanisms by which hormones can produce tumors. Peripheral tumors are of two kinds: those affecting non-hormone-secreting organs, which do not feed back (as with the mammary gland), and those affecting peripheral hormone-secreting organs, which do. The best example of the former is the mammary tumor, and good examples of the second type are thyroid and ovarian tumors. Other tumors which are hormonally related include adrenal tumors which are unique in that they can give rise to four or more types of tumors - estrogen, androgen, glucocorticoid, and mineralocorticoid secreting - and in that they have different types of inductive mechanisms. Renal cortical carcinomas are induced by estrogens in male hamsters. Human placental lactogen stimulates carcinogenesis in young rats. It promotes mammary tumorigenesis during pregnancy, both directly and indirectly, through its promotion of progesterone secretion by the ovary. Thyrocalcitonin is the hypocalcemic polypeptide hormone secreted by the medullary cells of the thyroid. These cells can give rise to medullary thyroid carcinoma. (286 Refs)

23. SEX HORMONES AND GYNAECOLOGICAL CANCER.

Scott JS
Dept. Obstetrics and Gynaecology, Leeds Maternity Hosp., Leeds LS2 9NG, England
Br Med J; 284(6330):1657-1658 1982

The balance of risks and benefits of sexual intercourse is discussed in relation to cervical, breast, ovary, and endometrial cancers. Sexual activity may increase the rate of cervical cancer, but pregnancy and lactation aid in prevention of other gynecological cancers. Oral contraceptives and hormonal replacement may play a role in prevention of some cancers, but other, possibly negative effects have not yet been assessed. (16 Refs)

24. MODULATION OF PROSTAGLANDIN SYNTHESIS AND TUMOR PROMOTION.

Fischer SM, Slaga TJ
Oak Ridge Natl. Lab., Oak Ridge, TN
Proceedings of the International Conference on Prostaglandins and Cancer, held in Washington, DC, August 31, 1981: Available from National Technical Information Service, Springfield, Va, as DE82002793:, 10 pp., 1981.

Studies are described which examine the role of prostaglandins in tumor promotion. These and other metabolites of arachidonic acid metabolism are not tumor promoters themselves, but play an integral part in the underlying mechanism of tumor promotion. (Author abstract)

25. METABOLISM OF CHEMICAL CARCINOGENS.

Weisburger JH, Williams G
American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Chemical carcinogens are defined by their ability to induce tumors, four types of response have generally been accepted as evidence of tumorigenicity. These include an increased incidence of the tumor types occurring in controls, the occurrence of tumors earlier than in controls, the development of types of tumors not seen in controls, and an increased multiplicity of tumors in individual animals. Examples of the genotoxic carcinogen class include alkylating agents which are activation independent, aromatic amines and polycyclic aromatic hydrocarbons which are activation-dependent, and metals. Examples of the epigenetic carcinogen class include plastics and asbestos, estrogen, androgen, purine analog, and phorbol ester. Promotors are agents that increase the tumorigenic response to a carcinogen when applied after the carcinogen. Genetic factors, sex and endocrine status, age, diet, activities of intestinal flora, the presence of other chemicals, the mode and frequency of exposure, and numerous other factors influence the variation in carcinogen metabolism. Research during the last few decades has pinpointed natural products as major causes of cancer in humans in various parts of the world. (486 Refs)

26. ENDOMETRIOSIS AND CANCER: CERTAIN COMMON FEATURES OF PATHOGENESIS AND BASIC PRINCIPLES OF TREATMENT.

Baskakov VP, Tsvelev IuV
S. M. Kirov Military Medical Acad., Leningrad, USSR
Vopr Onkol; 28(3):45-51 1982

Such features as single-phase cycling, endocrine infertility endometriosis with concomitant endometrial hyperplasia, endometrial carcinoma and endometriosis with concomitant uterine myoma and proliferative processes in the mammary glands as well as hormono-metabolic disorders frequently occur both in endometriosis and endometrial carcinoma and, therefore, suggest that pathogenesis of these hormone-dependent diseases has something in common. It was established experimentally that the likelihood of proliferation development and malignancy in the endometrium is great, when it is dislocated and, particularly, when hormonal disorders occur. An autoimmune nature of endometriosis is suggested. The similarity and differences in diagnosis of endometriosis and some types of cancer as well as common principles of treatment of the diseases are discussed. It is recommended in conclusion that patients with endometriosis of the uterus, ovary and other sites should be referred to a group at high risk for cancer. (Author abstract) (30 Refs) (In RUS)

27. CANCER OF CORPUS UTERI.

Kiriushchenkov AP
Moscow, USSR
Med Sestra; (4):54-58 1982

Etiology, diagnosis, treatment, and prevention of cancer of the corpus uteri (CCU) are discussed. The characteristic manifestations of CCU include bloody vaginal discharge during the postmenopause, uterine hemorrhage, and pain. Differential diagnosis between CCU and cervical cancer, endometriosis, uterine myoma, or hormone-active ovarian tumors can be made at cytological examination of the specimens of cervical mucosa. Treatment of CCU includes surgery and postoperative radiotherapy (Stage I), combined radiotherapy (Stages II and III), or palliative therapy (Stage IV). Hormone therapy with synthetic progestines can be used in the patients with recurrent and metastatic tumors. (no Refs) (In RUS)

28. ENDOCERVICAL CHANGES IN THE GUINEA PIG AFTER TREATMENT WITH 17-BETA-OESTRADIOL AND 9,10 DIMETHYLBENZANTHRACENE.

Thomas JA, Dallenbach FD
Dept. Pathology, St. John's Medical Coll., Bangalore 560 034, India
Adv Exp Med Biol; 144:281-284 1982

The possible synergistic effect of exogenous estrogen (17-beta-estradiol) and 9,10-dimethylbenzanthracene on guinea pig endocervices was investigated. Electron microscopy showed membrane thickening, mild dysplasia, and mucus cell differentiation and combined mucus and squamous cell differentiation. The well differentiated mucus cells contained excessive amounts of mucus; the little mucus released was by mucus-globus extrusion or release of partially or wholly membrane-bound mucus globule packets. (2 Refs)

29. VASOPRESSIN: ACTION OF WRK-1 RAT MAMMARY TUMOR CELLS.

Monaco ME, Kohn PH, Kidwell WR, Strobl JS, Lippman ME

Veterans Admin. Hosp., 16 West, 408 First Ave., New York, NY, 10010

JNCI; 68(2):267-270 1982

WRK-1, a cell line in long-term culture derived from a 7,12-dimethylbenz[a]anthracene-induced rat mammary tumor, responds to physiologic concentrations of vasopressin with increased precursor incorporation into phospholipids and with increased protein accumulation. Because vasopressin has been reported to be a potent mitogen for HeLa cells and 3T3 cells, a study was conducted to determine whether it could act as a mitogen for WRK-1 cells. Under no conditions was a clear-cut mitogen response to vasopressin demonstrated. (Author abstract) (14 Refs)

30. PROSTAGLANDIN ENDOPEROXIDE SYNTHETASE-DEPENDENT COOXIDATION OF (+-)-TRANS-7,8-DIHYDROXY-7,8-DIHYDROBENZO(A)PYRENE IN C3H/10T1/2 CLONE 8 CELLS.

Boyd JA, Barrett JC, Eling TE

(c/o Eling) Lab. Pulmonary Function and Toxicology, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709

Cancer Res; 42(7):2628-2632 1982

The proximate form of the carcinogen benzo(a)pyrene, (+-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene (BP-7,8-diol), is cooxidized during the oxidation of arachidonic acid to prostaglandins by prostaglandin endoperoxide synthetase (PES). This enzyme can oxidize BP-7,8-diol to the reactive intermediate (+-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a) pyrene, which binds covalently to macromolecules, is mutagenic in bacterial test systems, and forms 7,8,9,10-tetrahydroxy-7,8,9,10-tetrahydrobenzo(a)pyrene (BP-tetrol) isomers. We have examined the cooxidation of BP-7,8-diol in an intact cell culture system of C3H/10T1/2 clone 8 mouse embryo fibroblasts, in which both the mixed-function oxidase and PES systems are present. When BP-7,8-diol is incubated for 72 hr with approx 10(6) confluent cells, high-performance liquid chromatography analysis of the organic extractable products reveals all four pairs of BP-tetrols, with those from (+-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a) pyrene predominating. The addition of arachidonic acid (100 uM) produced a two- to three-fold increase in the formation of BP-tetrols from (+-)-7beta,8alpha-dihydroxy-9alpha,10alpha-epoxy 7,8,9,10-tetrahydrobenzo(a) pyrene, while the metabolism to BP-tetrols from (+-)-7beta,8alpha-dihydroxy-9beta,10beta-epoxy-7,8,9,10 tetrahydrobenzo(a) pyrene was unchanged. The addition of the PES inhibitor indomethacin (100 uM) completely eliminated this stimulation. Cell transformation assays were carried out under the same conditions. The addition of arachidonic acid resulted in a 10-fold increase in foci formation, while indomethacin inhibited the increase in foci formation by 70%. These results suggest that cooxidation of BP-7,8-diol to reactive intermediates by PES can occur in an intact cell system if stimulated with arachidonic acid. In addition to mixed-function oxidase-dependent activation of carcinogens, the cooxidation of chemicals to reactive metabolites during prostaglandin biosynthesis may also play a role in carcinogenesis. (Author abstract) (26 Refs)

31. COOXIDATION OF THE CLINICAL REAGENT 3,5,3'5'-TETRAMETHYLBENZIDINE BY PROSTAGLANDIN SYNTHASE.

Josephy PD, Mason RP, Eling T

Lab. Pulmonary Function and Toxicology, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709

Cancer Res; 42(7):2567-2570 1982

Prostaglandin synthase catalyzes the oxidation of arachidonic acid to prostaglandin H2 via a hydroperoxide intermediate, prostaglandin G2. The prostaglandin synthase system cooxidizes 3,5,3'5'-tetramethylbenzidine (TMB), a derivative of the human carcinogen benzidine, to colored products. This process is arachidonic acid dependent and indomethacin sensitive. The reaction is also supported by hydroperoxides, and, in this case, indomethacin has no effect. This suggests that the cooxidation is mediated by the hydroperoxidase activity of prostaglandin synthase. The products of TMB oxidation by this system are the same as those obtained with lactoperoxidase and H2O2 or with horseradish peroxidase and H2O2. The initial products of TMB oxidation are the TMB radical cation and a charge-transfer complex composed of TMB and its two-electron (diimine) oxidation product. The TMB radical cation was identified by electron spin resonance spectroscopy. Ascorbic acid reduces the products, regenerating the parent compound. (Author abstract) (22 Refs)

32. ENHANCEMENT OF DMBA INDUCED MAMMARY TUMOURS BY INTERMITTENT WHOLE BODY HYPERTHERMIA (42 C).

Lahiri T, Deomina N, Dedov II, Lahiri P

Chittaranjan Natl. Cancer Res. Centre, Calcutta, India

Endocrinol Jpn; 28(5):569-574 1981

Effects of intermittent whole body hyperthermia (42 C) on dimethyl benz-anthracene (DMBA)-induced rat mammary tumors were determined in terms of tumor growth, plasma hormone levels, and activity of pituitary prolactin cells. Female Wistar (50-55 days old) rats were used. Heat exposure resulted in significant growth stimulation of the tumors in the majority (16/20) of heat-treated rats, compared to rats maintained at 25 C. The growth of tumors was generally intensified after 2-3 wk of heat stress and at the end of 6 wk an approx seven-fold increase in tumor vol was observed. Histological examination revealed that 18/20 animals in the control group and 17/20 in the treated group had adenocarcinoma type tumors. Other tumors were fibroadenomas and they were not included into the study. Body wt and wt of adrenal glands in heat-exposed rats were increased, while the wt of uterus and thymus was decreased. Plasma estradiol level in heat stressed animals was lowered while values for total thyroxine and thyroid stimulating hormone showed no fluctuation. Serum prolactin level was significantly increased in the heat exposed group. An electron microscopy study of prolactin cell activity of pituitary revealed that in heat stressed animals the activity was greater than in rats maintained at room temperature. Results indicated that whole body hyperthermia definitely enhances DMBA-induced mammary tumors in rats and the differences in response pattern might be related to the mode of heat application, etiology, or hormonal sensitivity of tumors. (20 Refs)

33. INCREASED INDUCTION OF SISTER CHROMATID EXCHANGE BY DIETHYLSTILBESTROL IN LYMPHOCYTES FROM PREGNANT AND PREMENOPAUSAL WOMEN (MEETING ABSTRACT)

Hill AB, Wolff S
University of California, Berkeley, CA
Am J Hum Gen; 33(6):106A 1981

Cultures of whole blood from pregnant women (4-6 months), premenopausal women, postmenopausal women, and normal men were grown in the presence of varying concentrations (1 x 10(-5) M, 2 x 10(-5) M, and 4 x 10(-5) M) of diethylstilbestrol (DES), a synthetic estrogen and known carcinogen. DES induced sister chromatid exchanges (SCEs) in lymphocytes from pregnant and premenopausal women, but had only a small effect at the highest concentration (4 x 10(-5) M) in lymphocytes from men and postmenopausal women. At all concentrations, the average number of SCEs was consistently higher in lymphocytes from pregnant women than in those from premenopausal women. In lymphocytes from both men and pregnant women, DES strongly inhibited cell cycling, but induced polyploidy only in lymphocytes from the women. Cultured lymphocytes from pregnant women exposed to varying concentrations (1 x 10(-6) M, 5 x 10(-6) M, 1 x 10(-5) M, and 5 x 10(-5) M) of estradiol, a natural estrogen, did not show an increase in SCEs, demonstrating that DES's ability to induce SCEs is not a property associated with all estrogens. (no Refs)

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34. PITUITARY RESPONSES TO THYROTROPIN-RELEASING HORMONE AFTER TREATMENT WITH THE BREAST CARCINOGEN NITROSOMETHYLUREA: INHIBITION OF PROLACTIN BUT NOT THYROTROPIN RELEASE.

Kieffer JD, Maloof F, Vickery AL, Mover H, Downing M, Ridgway EC
Thyroid Unit, Massachusetts General Hosp., Boston, MA, 02114
Endocrinology; 110(6):1892-1896 1982

N-Nitrosomethylurea (NMU) is a widely used experimental breast carcinogen. The present report describes the effects of NMU on the plasma PRL and TSH increases in response to exogenous TRH. Female Buffalo rats, 75-80 days old, were given a single ip injection of NMU (10 mg/100 g) or vehicle. At various times after injection, NMU-treated rats and vehicle-injected controls were tested with exogenous TRH (625 ng/100 g, ip). Groups of four to six rats were bled at 10, 20, 30, 45, and 60 min after TRH and at 10 min after saline (baseline group). The response to TRH (delta) was determined by subtracting the mean plasma PRL or TSH level of the baseline group from the mean peak level observed after TRH. For four separate control experiments, deltaPRL averaged 104 +-19 ng/ml (mean +- SE). At 20 hr, 42 hr, 6 days, and 2, 3, 4, 8, and 12 wk after NMU, deltaPRL was 87, 0, 0, 16, 10, 3, 49, and 65 ng/ml, respectively. deltaPRL was statistically significant in all four control experiments, and remained significant at 20 hr after NMU. However, from 42 hr through 4 wk, no significant deltaPRL occurred. A significant deltaPRL reappeared at 8 and 12 wk, the approximate time of appearance of the first palpable breast cancers. Pituitary PRL concentrations (micrograms PRL per mg protein) were significantly lower in NMU-treated groups than in vehicle-treated controls at 42 hr, 3 wk, and 12 wk. In contrast to its marked inhibitory effect on deltaPRL, NMU had no effect on deltaTSH. This is consistent with the hypothesis that treatment with NMU resulted in a selective impairment of pituitary PRL-secreting cells. Moreover, our data show that the plasma PRL response to TRH was inhibited at times after NMU when pituitary PRL was not significantly depleted. This observation is in accord with the concept of impairment of either TRH receptor binding or events which couple receptor binding and hormone release. (Author abstract) (38 Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Accetta PA 9
Ahir S. 18
Alvarez J. 13
Ampy FR 18
Barrett JC 30
Baskakov VP 26
Beauregard H. 1
Becker FF 20
Blot WJ 2
Boyd JA 30
Burns PE 2
Chabner B. 12
Cleroux R. 1
Cohen M. 12
Colombo E. 11
Dallenbach FD 28
Dallenbach-Hell 4
Danforth D. 12
Danguy A. 16
De Muylder X. 1
DeMoss E. 12
Decarli A. 11
Dedov II 32
Deomina N. 32
Downing M. 34
Eling T. 31
Eling TE 30
Engle RL 3
Finkelstein JA 19
Fischer SM 24
Franceschi S. 11
Fraumeni JF 2
Furth J. 22
Gallus G. 11
Gardner WA 9
Gratton NM 1
Greenblatt RB 5
Habs M. 17
Hayry P. 10
Helmrich SP 3
Heston WE 21
Heuson JC 16
Hill AB 33
Hill MJ 6
Hopfner-Hallika 10
Jenicek M. 1
Josephy PD 31
Kaufman DW 3
Kidwell WR 29
Kieffer JD 34
Kiriushchenkov 27
Kohn PH 29
La Vecchia C. 11
Lahiri P. 32
Lahiri T. 32
Leclerq G. 16
Lee IM 19
Lee JA 7
Lees AW 2
Legros N. 16
Lichter A. 12
Lippman M. 12
Lippman ME 29
Lombard LF 14
Loring JM 15
Lotstra F. 19
Lubin JH 2
Maheux R. 1
Maloof F. 34
Mangioni C. 11
Mason RP 31
May C. 2
McGuire WL 8
Miettinen OS 3
Mohla S. 18
Monaco ME 29
Morris LE 2
Mover H. 34
Naylor PH 15
Nezhat C. 5
Reitamo JJ 10
Ridgway EC 34
Rosenberg L. 3
Rosenshein NB 3
Samaras C. 5
Schmahl D. 17
Schottenfeld D. 3
Scott JS 23
Shapiro S. 3
Sivula A. 10
Slaga TJ 24
Slone D. 3
Steggles AW 19
Stolley PD 3
Storer BE 7
Strobl JS 29
Sufrin G. 13
Swaneck G. 13
Tamarkin L. 12
Thomas JA 28
Tognoni G. 11
Totterman S. 10
Tsvelev IuV 26
Van Campenhout 1
Vanderhaeghen J. 19
Vasquez J. 5
Vickery AL 34
Villee CA 15
Wagner G. 17
Weisburger JH 25
Williams G. 25
Wolff S. 33

NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY OF POLYBROMINATED BIPHENYLS (PBBS) IN DOMESTIC AND LABORATORY ANIMALS.
Damstra T, Jurgelski W, Posner HS, Vouk VB, Bernheim NJ, Guthrie J, Luster M, Falk HL
Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 22709
Environ Health Perspect; 44():175-188 1982

2. CHLOROFORM: A REVIEW OF ITS METABOLISM, TERATOGENIC, MUTAGENIC, AND CARCINOGENIC POTENTIAL.
Davidson IW, Sumner DD, Parker JC
(c/o Parker) ECAO, Environmental Protection Agency, MD-52, Research Triangle Park, MD, 27711
Drug Chem Toxicol; 5(1):1-87 1982

3. FORMALDEHYDE IN PRESENT-DAY ENVIRONMENTAL TOXICOLOGY.
Beritic T, Kovac S, Dimov D
Odjel za profesionalne bolesti, Institut za medicinska istrazivanja i medicinu rada, Zagreb, Yugoslavia
Arh Hig Rada Toksikol; 32(4):363-395 1981
In SCR

4. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.
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Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

5. CURRENT VIEWS ON HORMONES AND BREAST CANCER.
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J Surg Oncol; 20(2):115-118 1982

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10. IDENTIFYING THE HEALTH RISKS FROM VERY LOW-DOSE SPARSELY IONIZING RADIATION.
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Am J Public Health; 72(6):585-588 1982

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13. RADIATION-INDUCED VASCULAR INJURY AND ITS RELATION TO LATE EFFECTS IN NORMAL TISSUES.
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Chemical Pathology Lab., Dept. Pathology, Univ. Texas Medical Branch, Galveston, TX

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Dept. Pharmacology, Univ. Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands

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41. METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS IN PLACENTA.

Juchau MR, Chao ST, Namkung MJ

Dept. Pharmacology, Sch. Medicine, SJ-30, Univ. Washington, Seattle, WA, 98195

Adv Exp Med Biol; 136(partA):555-573 1982

MODIFICATION OF CARCINOGENESIS

42. THE INTESTINAL ENZYMATIC BIOTRANSFORMATION SYSTEM: POTENTIAL ROLE IN PROTECTION FROM COLON CANCER.

Hoensch HP, Hartmann F

Medizinische Universitatsklinik, D-7400 Tubingen, W. Germany

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VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

43. THE ONCOGENIC CIRCLE CLOSES.

Rigby PW

Imperial Coll. Science and Technology, London SW7 2BZ, England

Nature; 297(5866):451-453 1982

44. ANALYSIS OF CASES OF HEPATIC CELL CARCINOMA THAT TRANSFORMED FROM VIRAL HEPATITIS.

Ichida F, Honma A, Soga K

Third Dept. Internal Medicine, Niigata Univ. Sch. Medicine, Niigata, Japan

Nippon Rinsho; 40(2):468-477 1982

In JPN

45. ROLE OF VIRUSES IN THE INDUCTION OF PRIMARY INTRACRANIAL TUMORS.

Walsh JW, Zimmer SG, Perdue ML

Div. Neurosurgery, Univ. Kentucky Medical Center, 800 Rose St., Lexington, KY, 40536

Neurosurgery; 10(5):643-662 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

46. TRANSLATION OF PHARMACOKINETIC/BIOCHEMICAL DATA INTO RISK ASSESSMENT.

Dietz FK, Reitz RH, Watanabe PG, Gehring PJ

Toxicology Res. Lab., Health and Environmental Sciences, Dow Chemical, 1803 Building, Midland, MI, 48640

Adv Exp Med Biol; 136(partB):1399-1424 1982

47. IN VITRO ASSAYS FOR THE DIFFERENTIATION OF TUMOR PROMOTORS FROM CARCINOGENS AFTER ROUTINE CARCINOGENESIS BIOASSAYS (MEETING ABSTRACT)

Ward JM, Rice JM

Frederick Cancer Research Center, Frederick, MD

Second Annual Meeting of the Society of Environmental Toxicology and Chemistry, November 22-25, 1981, Arlington, Virginia. Society of Environmental Toxicology and Chemistry 150 pp., 1982.

48. ENVIRONMENTAL CARCINOGENS: SELECTED METHODS OF ANALYSIS. VOLUME 4. SOME AROMATIC AMINES AND AZO DYES IN THE GENERAL AND INDUSTRIAL ENVIRONMENT.

Egan H, Fishbein L, O'Neill IK, Castegnaro M, Bartsch H

Lab. Government Chemist, London, England

IARC Sci Publ (40): 347 pp., 1981.

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HORMONAL CARCINOGENESIS

SERIES CK05 No. 82/11

NOVEMBER, 1982

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In this issue:

- ORAL CONTRACEPTIVES AND HUMAN CANCER 1-2
- ORAL CONTRACEPTIVES AND HUMAN HEPATIC ADENOMA 3
- ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER 4-7
- MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES 8-13
- MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES 14-15
- HORMONAL CARCINOGENESIS IN ANIMALS 16-20
- REVIEWS AND OTHER RELATED STUDIES 21-26

ORAL CONTRACEPTIVES AND HUMAN CANCER

1. PRE- AND POSTMENOPAUSAL BREAST CANCER.

Najem GR, Rush BF, Miller FW, Dimarco PE, Roellke SE, Grobstein N, Levitt JW

Dept. Preventive Medicine, MSB-F516, Univ. Medicine and Dentistry of New Jersey, 100 Bergen St., Newark, NJ, 07103

Prev Med; 11(3):281-290 1982

Age at menarche, parity, age at first full-term birth, breast feeding patterns, age at menopause, and history of oral contraceptive use were investigated in a case-control study involving 60 breast cancer patients and 125 matched controls from the same New Jersey screening population. Significant associations were found between the presence of other cancers in relatives, oral contraceptive use, and weight of subjects, and incidence of breast cancer, but no significant associations were found between age at menarche, age at first full-term birth, age at menopause, parity, or menopausal status. (25 Refs)

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2. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.

Brzezinski A, Schenker JG

Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel

Isr J Med Sci; 18(4):433-438 1982

The possible association of oral contraceptives (OC) and menopausal estrogens (ME) on development of breast cancer is reviewed. The high incidence of breast cancer concurrent with extensive OC-ME usage, considered together with the relatively high hormone dependence of breast tumors and the placement of the breast as a target organ in the estrogen-progesterone hormonal pathways supports this association. Theories of the hormonal etiology involve estriol, progesterone, androgens, and the pineal gland; however, the specific hormonal etiology is unclear. Most studies have demonstrated significantly decreased risk of benign breast disease in women using OC. Since increased parity and early first birth are potentially protective conditions for breast cancer, OC, by simulating pregnancy, may exert a protective effect. The incidence of benign breast disease appears to be inversely related to the amount of progesterone in different OC. No significant overall increase in the risk of breast cancer has been demonstrated among users of OC. However, specific subgroups in which an increased risk was shown have been identified, including women with previous biopsy of benign breast disease. Evidence is available associating ME with an increased risk of endometrial carcinoma. Recent studies have demonstrated a positive association between ME and breast cancer. Caution is suggested in long-term use of OC and the continuous use of ME for periods greater than 10 yr should be reconsidered. (57 Refs)

ORAL CONTRACEPTIVES AND HUMAN HEPATIC ADENOMA

3. LIVER DISEASES DUE TO HORMONAL CONTRACEPTIVES.

Lie TS

Chirurgische Klinik und Poliklinik, Universitat, Sigmund-Freud-Str. 25, D-5300 Bonn 1, W. Germany

MMW; 124(20):489-494 1982

A review of hepatic diseases concerning the use of oral contraceptives shows a considerable increase in the incidence of benign hepatic tumors and precancerous conditions (adenoma, focal nodular hyperplasia and mixed benign tumors) since the introduction of oral contraceptives. Seventeen cases of malignant hepatic tumors (hepatocellular carcinoma in 16 and mixed tumor in 1) following the use of oral contraceptives for 1-11 yr were found in the literature. (82 Refs) (In GER)

ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER

4. CLEAR CELL ADENOCARCINOMA OF THE VAGINA AND CERVIX IN BLACK FEMALES.

Johnston GA, Anderson D, Herbst AL, Hubby MM
Dept. Obstetrics and Gynecology, Ohio State Univ., 410 West 10th Ave., Columbus, OH, 43210
J Natl Med Assoc; 74(7):639-643 1982

Twenty-eight black females with clear cell adenocarcinoma of the vagina and cervix have been accessioned in the Registry for Research on Hormonal Transplacental Carcinogenesis. Most were born in the southern United States and histories of prenatal exposure to diethylstilbestrol were less frequent than with white patients. The characteristics of these cases were similar to those among whites in stage, variety of cell type, and patient survival. (Author abstract) (8 Refs)

5. BREAST TUMORS IN PATIENTS WITH HYPERPROLACTINEMIA.

Brown RW, Meehan C, Martin FI, Bhathal PS
(c/o Martin) Post Office, Royal Melbourne Hosp., Victoria, 3050, Australia
Cancer; 50(1):125-129 1982

The histology of breast lumps in five patients with hyperprolactinemia showed benign mammary dysplasia with vacuolation of acinar and duct lining cells. In two cases, foci of lobular development resembling lactating breast tissue were also noted. In the past, focal secretory change has been considered to be idiopathic, but these cases indicate a possible association with hyperprolactinemia. Among other causes hyperprolactinemia may be a manifestation of occult pituitary adenoma. Therefore it is suggested that patients with benign breast nodules showing focal secretory change should be screened for clinical and laboratory evidence of hyperprolactinemia. Although it is accepted that in mice and rats prolactin plays an important role in chemically induced mammary tumorigenesis, a consensus has not been reached with regard to its role in man. (Author abstract) (17 Refs)

6. ENDOGENOUS HORMONES AS A MAJOR FACTOR IN HUMAN CANCER.

Henderson BE, Ross RK, Pike MC, Casagrande JT
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Cancer Res; 42(8):3232-3239 1982

Hormone-related cancers account for almost 30% of all cancer cases in the United States. Data from animal experiments and from epidemiological and endocrinological studies in humans support the hypothesis that the individual hormones which control normal growth of target organs can also create the proper conditions for neoplastic transformation. The concept that hormones can cause, ie, increase the incidence of, human cancer is most developed for the four hormone-related cancers which are numerically the most important, namely, breast, prostate, endometrium, and ovary. Even for these sites, large gaps remain in our knowledge of the responsible hormones and the conditions which create the optimal opportunity for carcinogenesis. Although scanty, the available epidemiological evidence also suggests a hormonal role in the pathogenesis of testis cancer, thyroid cancer, and osteosarcoma. We believe that the primary prevention of all these cancers will probably depend on modification of the factors which affect the secretion and metabolism of the responsible hormones rather than on control of exposure to classical exogenous initiators. (Author abstract) (129 Refs)

7. RELATIONSHIP OF OBESITY TO BLOOD ESTROGENS.

Zumoff B
Div. Endocrinology and Metabolism, Dept. Medicine, Beth Israel Medical Center, New York, NY, 10003
Cancer Res; [illegible](8,Suppl):3289s-3294s 1982

It has become conventional wisdom that estrogenic stimulation of breast tissue has something to do with the causation of breast cancer and that the reason obesity is a risk factor for breast cancer is that obese women are hyperestrogenized. However, it has been very difficult to demonstrate that excessive exogenous estrogen increases the incidence of breast cancer, that endogenous estrogen excess is present in breast cancer, or that obese women are hyperestrogenized. We have examined the last question by measuring 24-hr mean plasma estrone and estradiol levels in the midfollicular phase in 18 healthy, regularly cycling, very obese (53 to 218% above ideal weight) women and 16 regularly cycling, age matched, nonobese control women. Unlike obese men, the obese women showed no significant elevation of either estrone or estradiol. Their av estrone level was 72 compared with 64 pg/ml in controls; their average estradiol level was 65 compared with 57 pg/ml in controls. In the combined group (obese plus nonobese), there was a significant correlation of percentage of deviation from ideal weight with plasma estrone ($y = 63 + 0.12x$; p less than 0.05) but not with estradiol. This correlation supports the current hypothesis that there is increased androstenedione/estrone conversion (ie, increased aromatase activity) in obesity. The reason plasma estrone levels are not significantly elevated in obese women is that the small amount derived from androstenedione is swamped by the much larger amount derived from ovarian secretion, which is apparently unaffected by obesity. Unless there is increased local formation of estrogens in the breast tissue of obese women, the absence of elevated plasma estrogens in them means that their breasts are not 'seeing' increased estrogen levels. Thus, endogenous hyperestrogenization is unlikely to be a causative factor of breast cancer in obese women. (Author abstract) (48 Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES

8. PROLACTIN RECEPTORS IN CULTURED RAT MAMMARY TUMOR CELLS. UNMASKING OF CELL SURFACE RECEPTORS BY ENERGY DEPLETION.

Costlow ME, Hample A
Dept. Biochemistry, St. Jude Children's Res. Hosp., Memphis, TN, 38101
J Biol Chem; 257(12):6971-6977 1982

The level of specific binding of 125I-labeled ovine prolactin to primary cultures of 7,12-dimethylbenzanthracene-induced rat mammary tumors can be increased 2-to 20-fold by a variety of chemically distinct respiratory inhibitors or uncouplers of oxidative phosphorylation. Independent of the type of inhibitor used, binding increases when the cellular ATP level is decreased by at least 70%. This change is due to an apparent increase in the number of binding sites. Receptor affinity (Kd = 4 x 10(-10) M) is not affected. The binding of 125I-labeled epidermal growth factor to tumor cells is not similarly altered. Primary cultures of normal mammary gland from perphenazine-stimulated rats and tumor tissue slices also show increased prolactin binding in the presence of these inhibitors. In contrast, binding to slices from lactating mammary gland, liver, ovary, adrenal gland, or kidney is unaffected. The low level of prolactin binding in untreated tumor cell cultures is not due to hormone degradation or rapid down-regulation of receptors. Electron microscope autoradiography indicates that in the presence of 2,4-dinitrophenol prolactin binding is limited to the cell surface. Sites that can be activated by energy depletion are also localized on the cell surface. Thus, prolactin receptors in proliferating normal and neoplastic rat mammary tissue exist in two forms on the cell surface, an active form that recognizes and binds prolactin and an inactive form that does not. When cellular ATP levels are normal, the inactive form predominates (2 to 20 inactive sites for each active site). When ATP levels are markedly decreased, receptors are converted to the active (binding) form. In target cells where prolactin is not trophic, inactive receptors are absent or energy depletion does not activate the binding sites. This pool of cryptic cell surface receptors may enable certain prolactin target tissues with the ability to rapidly change their level of available prolactin receptors and thus regulate their hormonal response. (Author abstract) (60 Refs)

9. RADIOTRACERS BINDING TO ESTROGEN RECEPTORS: I: TISSUE DISTRIBUTION OF 17 ALPHA-ETHYNYLESTRADIOL AND MOXESTROL IN NORMAL AND TUMOR-BEARING RATS.

Feenstra A, Nolten GM, Vaalburg W, Reiffers S, Woldring MG
(c/o Vaalburg) Dept. Nuclear Medicine, Univ. Groningen, Oostersingel 59, 9713 EZ Groningen, The Netherlands
J Nucl Med; 23(7):599-605 1982

Ethynylestradiol and moxestrol can be labeled with carbon-11 by introducing this positron emitter in the 17alpha-ethynyl group. To investigate their potential as radiotracers binding to estrogen receptors, we studied the tissue distribution of tritiated ethynylestradiol and moxestrol, with specific activities of 57 Ci/mmol and 77-90 Ci/mmol, respectively, in the adult female rat. At 30 min after injection, both compounds showed specific uptake in the uterus (% dose/g): 2.52 for ethynylestradiol and of 2.43 for moxestrol. A decrease of the specific activity to 6-9 Ci/mmol resulted in uterine uptakes of 1.60 and 2.10 respectively, for ethynylestradiol and moxestrol, at 30 min. In the female rat bearing DMBA-induced mammary tumors, specific uptake was also measured in the tumors, although the values were only 25-30% of the uterine uptake. Moxestrol showed a greater uptake selectivity in the tumors compared with ethynylestradiol. From this study we conclude that ethynylestradiol and moxestrol have good potential as tracers binding to mammary tumors that contain estrogen receptors. (Author abstract) (24 Refs)

10. STEROID HORMONE RECEPTORS IN THE RAT MAMMARY ADENOCARCINOMA INDUCED BY N-HYDROXY-N-2-FLUORENYLACETAMIDE.

Li SA, Malejka-Giganti D, Li JJ
Medical Res. Lab., Veterans Admin. Medical Center, Minneapolis, MN, 55417
JNCI; 69(1):41-45 1982

The steroid hormone receptors in N-2-fluorenylacetamide (2-FAA)- and N-hydroxy-2-FAA-induced mammary adenocarcinomas in outbred Sprague-Dawley rats were analyzed. Both 8S and 4S estrogen-binding components have been detected in cytosols of these tumors following sucrose gradient sedimentation in low salt. Competitive binding analyses of this binder indicated a specificity profile expected of an estrogen receptor. Both androgen and progesterone receptors were also present in the cytosols of these mammary tumors. While the androgen receptor sedimented in the 8S region of the gradient, the progestin binder appeared only as a 4S moiety under similar conditions. The relative concentrations of these receptors (expressed in fmol/mg protein +- SE) were: 17 beta-estradiol (28.6 +-4.1) greater than 5alpha-dihydrotestosterone (8.5 +-2.2) greater than progesterone (5.0 +-1.3). The progesterone receptor was increased at least eightfold in the mammary adenocarcinomas from ovariectomized rats that were treated with diethylstilbestrol for 6 days. Binding equilibrium data indicated K = 1.2-1.8 x 10(9) M-1 for the above cytoplasmic hormone receptor complexes (Ka, association constant). Although cytosols prepared from lactating mammary gland contained appreciable quantities of glucocorticoid receptor, only trace amounts were found in the mammary adenocarcinoma. (Author abstract) (33 Refs)

11. EVIDENCE FOR MICROSOME-MEDIATED COVALENT BINDING OF DIETHYLSTILBESTROL TO DNA OR NUCLEOTIDES (MEETING ABSTRACT).

Liehr JG, DaGue BB
University of Texas Health Science Center, Houston, TX, 77025
Proc Am Assoc Cancer Res; 23:916 1982

In order to examine the possible role of estrogenic hormones as initiators of carcinogenesis, binding of the synthetic estrogen diethylstilbestrol (DES) to deoxynucleosides and calf thymus DNA was studied in an in vitro microsome-mediated reaction system. Binding levels were influenced by the reaction time, source of microsomes, and concentrations of DES, DNA, and microsomal cyt P450 (or P448) used in the reaction system. Reactions of 14C-DES (56 mCi/mmole) with 0.36 mM calf thymus DNA (heat denatured) or 3.3 mM dGMP catalyzed by phenobarbital-induced rat liver microsomes for 2.5 hrs produced 1300 and 50 adducts/ 10(6) nucleotides x nmole cyt P450), respectively. Binding of DES to DNA and dGMP in the presence of boiled microsomes was 1% and 10%, respective, of that found in active microsome catalyzed reactions. Evidence for the covalent nature of DES binding to DNA and deoxynucleotides was obtained from the persistence of bound radioactivity after exhaustive extraction of reactions with organic solvents and, in the case of DNA, multiple precipitations from ethanol. Furthermore, it has been possible to separate by reverse phase high pressure liquid chromatography unreacted deoxynucleosides and the radioactive DES-deoxynucleosides obtained from organic solvent-extracted and alkaline phosphatase-treated binding reactions of 14C-DES and deoxynucleotides. (no Refs)

12. GLUCOCORTICOID RECEPTORS (GR) IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA (ALL) (MEETING ABSTRACT).

Pui CH, Costlow ME, Chen L, Murphy SB, Dahl GV
Division of Hematology/Oncology, St. Jude Children's Research Hospital, Memphis, TN, 38101
Proc Am Soc Clin Oncol; 1:C-533 1982

We have studied GR levels in leukemic blasts of 174 children with newly diagnosed ALL over the past 3 years. A whole-cell [3H]-dexamethasone binding assay was used to measure GR levels. All samples were freshly prepared from bone marrow aspirates and contained greater than 90% blasts. Receptor levels varied from 3,300 to 79,000 sites/cell (median 18,000). Low GR levels were associated with recognized high-risk clinical features at diagnosis: high WBC count, T-cell surface markers, E rosette +, age less than 2 or greater than 10 yr (P less than 0.001), black race, CNS leukemia and mediastinal mass. GR levels were not related to FAB classification, sex, in vitro [3H]thymidine labeling index or quantitative terminal deoxynucleotidyl transferase levels. Similar results were obtained when GR levels were analyzed as a continuous variable. Excluding 36 patients with T-cell disease, low GR levels were still associated with age less than 2 yr and black race. The relationship between GR levels and prognosis was analyzed in 43 patients treated according to our Total Therapy IX Protocol and followed for greater than 26 mo. Patients were randomized to 3 treatment groups at diagnosis. There was no significant difference in the distribution of patients with high or low GR levels among the treatment groups. Seven of 19 patients with less than or equal to 16,000 GR sites/cell failed induction, compared to only 1 of the 24 patients with higher levels. Of patients who achieved remission, 8 of 12 with low GR levels have relapsed in contrast to 6 of 23 with higher levels. Excluding 16 patients with high-risk features, low GR levels were still associated with a higher risk of relapse. (1 Ref)

13. AN EPIDEMIOLOGIC STUDY OF BREAST CANCER IN POSTMENOPAUSAL WOMEN ACCORDING TO THE LEVEL OF ESTROGEN RECEPTOR IN THE TUMOR.

Hildreth NG
Yale University, New Haven, CT
Diss Abstr Int [B]; 42(12,pt1):4754-B 1982

This case-control study has examined the epidemiology of breast cancer with regard to the level of estrogen receptor in the tumor. Breast cancer cases and controls were postmenopausal women aged 45-74 years who were admitted to two hospitals in New Haven, Connecticut. A standardized structured questionnaire administered by trained interviewers was used to collect data on demographic variables, reproductive and menstrual histories, use of exogenous estrogens, family history of female cancers, body build indicators, and a history of certain illnesses and surgical procedures. All breast tumors were assayed similarly in one laboratory for estrogen receptor. An analysis of the cases alone identified five factors associated with the level of estrogen receptor in the tumor, the latter being considered both as a dichotomous (estrogen receptor positive versus estrogen receptor negative) and as a continuous (logarithm of the estrogen receptor concentration) variable. Tumors were more likely to be estrogen receptor positive and were more likely to have a higher mean estrogen receptor concentration among women with any of the following characteristics: nulliparity, having had a late age at first live birth, having had a history of benign breast disease, and having breastfed at least one child. Use of estrogen replacement therapy was associated with a greater likelihood of the tumor being estrogen receptor negative and having a lower mean estrogen receptor concentration. A case-control analysis distinguishing cases according to the estrogen receptor status of the tumor and focussing specifically on these five factors suggests that the epidemiology of estrogen receptor positive and estrogen receptor negative breast cancers may be dissimilar in some respects. With regard to the etiology of breast cancer, further support is provided for a central role of estrogens. (no Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: METABOLIC AND PHYSIOLOGIC STUDIES

14. THE CO-OXIDATION OF 2-AMINOFLUORENE DURING PROSTAGLANDIN BIOSYNTHESIS IN RAM SEMINAL VESICLE MICROSOMES (MEETING ABSTRACT).

Boyd JA, Eling TE
National Institute of Environmental Health Sciences, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:78 1982

The metabolism of the chemical carcinogen 2-aminofluorene (2-AF) during prostaglandin biosynthesis, using ram seminal vesicle microsomes as a source of prostaglandin endoperoxide synthetase (PES), was examined. 2-AF inhibited prostaglandin biosynthesis in a dose-dependent manner, as well as the peroxidatic co-oxidation of phenylbutazone, suggesting that 2-AF is both an inhibitor of PES and a reducing co-factor for the hydroperoxidase activity of PES. At a concentration of 100 uM, 2-AF was co-oxidized during prostaglandin biosynthesis to 2-nitrofluorene and 2,2'-bisazoxyfluorene, both of which were isolated and identified by co-chromatography and mass spectrometry. The formation of 2,2'-bis-azoxyfluorene indicated the formation of N-OH-2-AF as well. This 2-AF metabolism was dependent on the presence of the PES substrate arachidonic acid, inhibited by the PES inhibitor indomethacin, and was not observed using heat denatured microsomal protein. Preliminary data suggest that N-OH-2-AF is also a substrate for PES, and is metabolized to 2-nitrofluorene and 2,2'-bisazoxyfluorene as well. In addition, 2-AF was metabolized to a mutagenic metabolite(s), as measured by using RSV as an activating system in the Ames test. In summary, the above data indicate that the co-oxidation of 2-AF during prostaglandin biosynthesis in vitro results in the formation of N-OH-2-AF, the presumed ultimate carcinogenic metabolite of 2-AF and 2-acetylaminofluorene. (no Refs)

15. RESISTANCE OF TERMINAL DIFFERENTIATION IN PRECANCEROUS MAMMARY HYPERPLASIA (MEETING ABSTRACT).

McGrath CM, Soule HD
Michigan Cancer Foundation, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:904 1982

Acquired resistance to terminal differentiation is a crucial step in neoplastic transformation of cells that grow by differentiative renewal (eg mammary cells). We sought to determine if such resistance was already acquired at the precancerous stage of mammary cell transformation, and if it was associated with new responsivity to hormones normally controlling proliferation. Hyperplastic ductal and alveolar foci, induced by DMBA (dimethylbenzanthracene) and oncogenic viruses respectively, were isolated from Balb/c mouse mammary glands. Cells were pseudocloned from individual atypias on collagen-coated substrates and tested for accumulation of casein (a marker for end-point differentiation) in response to insulin (I), cortisol (F) and prolactin (M). Responsivity of differentiation-resistant and sensitive cells to mitogens was determined by replica plating corresponding colonies. Persistant precancerous hyperplasias, both ductal and alveolar, but not benign involutional hyperplasias, contained reduced numbers of cells responsive to IFM, when compared to normoplastic controls. Results of replica plating experiments in which proliferative responsivity of cells to epidermal growth factor (EGF) was measured autoradiographically, suggest that cells resistant to terminal differentiation are also more responsive to EGF. (no Refs)

HORMONAL CARCINOGENESIS IN ANIMALS

16. CHEMICAL HEPATOCARCINOGENESIS IN INFANT MICE FOLLOWING A SINGLE ADMINISTRATION OF TESTOSTERONE AT THE NEONATAL STAGE.

Toh YC

Dept. Physiology, Univ. New England, Armidale, New South Wales, 2351, Australia

IRCS Med Sci [Cancer]; 9(11):1044 1981

BALB/c mice were injected sc with 100 ug testosterone propionate at the age of 2 days, then fed a diet containing N-2-fluorenylacetamide (FAA) beginning at 1 wk of age qod to a total dose 10.5 mg. At the age of 1 yr, hepatocellular tumors were found in 21% of male mice given FAA, 11% of female mice given testosterone then FAA, and in none of the female mice given FAA without testosterone. Thus, a single injection of testosterone propionate to neonatal female mice enhanced carcinogenicity of FAA, although male mice still had a higher incidence of hepatic lesions. (5 Refs)

17. ESTRADIOL PROMOTION OF NEOPLASTIC LESIONS IN THE RAT VAGINA AFTER INITIATION WITH N-METHYL-N-NITROSOUREA (MEETING ABSTRACT).

Sheehan DM, Frederick CB, Branham WS, Heath JE

The National Center for Toxicological Research, Jefferson, AR, 72079

Proc Am Assoc Cancer Res; 23:925 1982

Estrogens share a number of biological properties with tumor promoters, and are reported to promote tumorigenesis in two estrogen target organs, the mammary gland and liver. Since the rat vagina is a well described estrogen target organ, we tested the hypothesis that estradiol (E2) is a tumor promoter for the vagina. Rats (CD) ovariectomized at 60 days of age were randomly assigned one week later to one of four treatment groups: 1) initiator only; 2) multiple initiator; 3) initiator-promoter; and 4) promoter only. The initiator was N-methyl-N-nitrosourea (MNU), a short-lived direct acting carcinogen, administered by vaginal instillation in a single dose of 0.25 mg in 75 ul isotonic phosphate buffer to groups 1 and 3. Group 2 received 4 weekly doses of 0.25 mg MNU. Silastic capsules containing E2 (5 mg/ml in 50 ul sesame oil) were implanted in animals of groups 3 and 4, one week after initiator treatment. Silastic implants provided sustained elevated E2 levels, shown by E2 radioimmunoassay and increased uterine weight. After 16 months, vaginal tumor incidence and type were: group 1, 0/9; group 2, 2/8 (papilloma, squamous cell carcinoma); group 3, 4/9 (polyps); group 4, 0/8. Polyps (2-18 mm) were composed of a fibrovascular stroma covered by squamous epithelium of varying thickness. A number of nonneoplastic lesions (groups 3 and 4) were due to E2 with or without MNU. The statistically significant incidence of polyps and their restriction to only the initiator-promoter group suggests that estrogens can promote tumorigenesis in the rat vagina. (no Refs)

18. MORPHOLOGICAL AND NEOPLASTIC TRANSFORMATION OF SYRIAN HAMSTER EMBRYO FIBROBLASTS BY DIETHYLSTILBESTROL AND ITS ANALOGS.

McLachlan JA, Wong A, Degen GH, Barrett JC
Transplacental Toxicology Section, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709

Cancer Res; 42(8):3040-3045 1982

A mammalian cell culture system using normal, diploid Syrian hamster embryo fibroblasts was used as a model to study the ability of diethylstilbestrol (DES) and related compounds to induce neoplastic transformation. Like benzo(a)pyrene, a known chemical carcinogen, DES (0.01 to 10 ug/ml) induces morphological transformation of Syrian hamster embryo fibroblasts in vitro; the transformed colonies were indistinguishable from colonies of benzo(a)pyrene-transformed cells. The morphologically transformed colonies derived from either benzo(a)pyrene- or DES-treated cells were tumorigenic when injected into newborn hamsters. At doses of 0.01 to 1 ug/ml for 48 hr, DES did not inhibit or stimulate cell proliferation. Structural analogous of DES were also tested in the Syrian hamster embryo transformation system. Like DES, tetrafluoro-diethylstilbestrol, dimethylstilbestrol, and cis,cis-dienestrolmorphologically transformed Syrian hamster embryo cells. The transformation frequency of dimethylstilbestrol was much less than that of DES, tetrafluorodiethylstilbestrol, or cis,cis-dienestrol. Hexestrol, dimethoxydiethylstilbestrol, and trans,trans-dienestrol did not transform these cells. No correlation could be demonstrated between reported estrogenic potency of the compounds and their cell-transforming capacity. Structure-activity relationships developed for these chemicals suggest that metabolism via specific pathways plays a role in DES-induced cell transformation. (Author abstract) (33 Refs)

19. ETHYLNITROSOUREA-INDUCED THYROID TUMORS IN RATS.

Ird EA, Smirnova IO
All-Union Cancer Res. Center, Moscow, USSR

Eksp Onkol; 4(3):68-70 1982

Effect of ethylnitrosourea (ENU: 30 mg/kg, ip) on thyroid carcinogenesis was studied in random-bred albino rats subjected to transplacental exposure to sex hormones. Estrogens and androgen were administered to pregnant females on Days 19, 20, and 21 of gestation, and the ENU was administered to the offspring when they were 16-20 days old or 4-6 mo old. The incidence of spontaneous thyroid tumors (solid and follicular adenomas) was 3%. Transplacental administration of the sex hormones, without administration of the ENU, induced thyroid tumors in 13-15% of the males and in 7-8% of the females; almost all of the rats developed solitary adenomas. ENU administration, without prior administration of sex hormones, induced thyroid tumors in 57% of the immature males and 58% of the immature females. Administration of the sex hormones prior to administration of the ENU did not affect the incidence of ENU-induced thyroid tumors in the immature males (40-50%) but reduced the incidence in the immature females (24-28%). ENU administered alone or in combination with sex hormones did not affect the incidence of thyroid tumors in the mature rats. (8 Refs) (In RUS)

20. ENHANCED AND REVERSED GROWTH IN VIVO OF A PREGNANCY-DEPENDENT MOUSE MAMMARY TUMOR (TPDMT-4) BY A GONADOTROPIN-RELEASING HORMONE AGONIST ANALOG.

Matsuzawa A, Yamamoto T
Lab. Animal Res. Center, Inst. Medical Science, Univ. Tokyo, P.O. Takanawa, Tokyo 108, Japan

Eur J Cancer Clin Oncol; 18(5):495-505 1982

TPDMT-4 pregnancy-dependent mammary tumors grow continuously in DDD female mice carrying pituitary isografts (PI) ectopically or bearing an sc 17beta-estradiol plus progesterone (EP) pellet. A gonadotropin-releasing hormone (GnRH) agonist (D-leucyl6, des-glycyl-NH210, prolyl-ethylamide9) GnRH (TAP-144), was examined for its antitumor activity in these experimental systems. TAP-144 was injected ip at doses of 300 and 600 ug 6x weekly, when tumors grew to significant sizes. TAP-144 enhanced tumor growth during the first 2 weeks and subsequently reversed it in a dose-related manner in PI-bearing mice. The agonist did not affect tumor growth in the absence of ovaries in these mice. In ovariectomized mice, TAP-144 enhanced EP pellet-induced tumor growth but never reversed it. In ovariectomized, PI-bearing mice. TAP-144 first enhanced and subsequently reversed tumor regrowth induced by ovarian grafts to a greater extent when commencing it simultaneously with ovarian grafting than 30 days before it. The agonist also exerted the dual effects on TPDMT-4V ovarian-dependent subline tumors in the absence of PI. In TAP-144-treated mice, enhanced tumor growth was related to many solid corpora lutea in ovaries and fully developed mammary glands, but reversed growth was related to atrophied luteal components and mammary glands. The results suggest that TAP-144 enhances tumor growth first via its stimulative action on the pituitary-ovarian axis and causes tumor regression later via its direct inhibitory action on ovaries. (Author abstract) (31 Refs)

REVIEWS AND OTHER RELATED STUDIES

21. BIOCHEMISTRY OF AROMATASE: SIGNIFICANCE TO FEMALE REPRODUCTIVE PHYSIOLOGY.

Ryan KJ
Lab. Human Reproduction and Reproductive Biology, Harvard Medical Sch., Boston, MA, 02115

Cancer Res; 42(8,Suppl):3342s-3344s 1982

The formation of estrogens in mammals via aromatase involves the relatively unique capacity to form an aromatic ring de novo in contrast to most other aromatic substances (essential amino acids) which are obtained only in the diet. The reaction is the only example of a cytochrome P-450 system which resides in both the mitochondrial and microsomal fractions of the cell. It occurs widely throughout the body in diverse tissues and functions via both de novo synthesis and transformation of prehormones (androstenedione and testosterone). It is found widely in animal species in both the brain and gonads even in phylogenetically primitive species. Placental aromatase appears to be associated with the evolution of viviparity and an extended gestational period in utero. Follicular aromatase which is dependent upon follicle-stimulating hormone stimulation appears to be essential for oogenesis, ovulation, and normal luteal functions while central nervous system aromatase serves to determine sexual behavior and the neurohormonal link to the hypothalamus and pituitary for ovarian cyclicity.

While estrogens are the key to pituitary, breast, and endometrial growth and development, this hormone is one of the few examples of an endogenous steroid that has been implicated as a carcinogen or a stimulant for carcinogenesis. (Author abstract) (18 Refs)

22. SIDE EFFECTS OF DRUGS. ANNUAL 6. A WORLDWIDE YEARLY SURVEY OF NEW DATA AND TRENDS.

Dukes MN, Elis J
Netherlands Commitee for the Evaluation of Medicines, Ministry of Health, Koopmanstraat 1, 2288 BC Rijswijk, The Netherlands
Side Eff Drugs Annu 6: 478 pp., 1982.

Current information relating to adverse drug reactions and interactions from the clinical point of view is presented. Drugs are classified according to primary field of application or for the properties for which they are most generally recognized. In borderline cases some supplementary discussion has been included relating to secondary fields of application. Fixed combinations of drugs are dealt with according to their most characteristic component. Agents covered include CNS stimulants and anorectic agents; antidepressants; lithium; social drugs; hypnotics; sedatives; anticonvulsants; opioid analgesics; narcotic antagonists; antipyretic analgesics; anti-inflammatory analgesics and drugs used in rheumatoid arthritis and gout; general anesthetics; therapeutic gases; local anesthetics; muscle relaxants; drugs affecting autonomic functions or the extrapyramidal system; drugs used on the skin; antihistamines; drugs used in bronchial asthma and cough; cardiac glycosides; drugs used in dysrhythmias; anti-anginal and beta-adrenoreceptor blocking drugs; drugs acting on the peripheral circulation; hypotensive drugs; diuretic drugs; metals; metal antagonists; antiseptic drugs and disinfectants; penicillins; cephalosporins; tetracyclines; other antibiotic drugs; antifungal drugs; antiprotozoal drugs; sulfonamides; miscellaneous antibacterial and antiviral drugs; drugs used in tuberculosis and leprosy; anthelminthic drugs; enzymes; enzyme inhibitors; immunologic preparations; blood and blood products; iv infusions (soln and emulsions); drugs affecting blood clotting, fibrinolysis, and hemostasis; gastrointestinal drugs; drugs used in the management of gallstones; vitamins; corticosteroids; corticotrophins; sex hormones and related compounds including oral contraceptives; thyroid and antithyroid drugs; insulin; glucagon; oral hypoglycemic drugs; miscellaneous hormones and prostaglandins; drugs affecting lipid metabolism; cytostatic and immunosuppressive drugs; radiologic contrast media; drugs used in ocular treatment; drugs used in non-orthodox medicine; and miscellaneous drugs. (3118 Refs)

23. EFFECT OF GLUCAGON ON AMINO ACID TRANSPORT AND CYCLIC ADENOSINE 3':5'-MONOPHOSPHATE PRODUCTION IN RAT HEPATOMA CELL LINE MCA-RH 8994 IN CULTURE.

Kelley DS
Dept. Biochemistry, West Virginia Univ., Sch. Medicine, Morgantown, WV, 26506
Cancer Res; 42(8):3116-3119 1982

The rates of alpha-aminoisobutyrate (AIB) transport and cyclic adenosine 3':5'-monophosphate (cAMP) production in response to glucagon (2 x 10(-7) M) have been determined in monolayer cultures of hepatoma cell line 8994 (refes to hepatoma cell line McA-RH 8994) under three different calcium treatments. The calcium treatments were: (a) control, cultures maintained in calcium-containing medium without prior calcium depletion; (b) calcium depleted, cultures maintained in calcium-free medium after treatment with ionophore A23187 and ethylene glycol bis(beta-aminoethyl ether)-N,N'-tetraacetic acid; (c) calcium repleted, cultures maintained in calcium-containing medium after treatment with A23187 and ethylene glycol bis (beta-aminoethyl ether)-N,N'-tetraacetic acid. In the control cultures, glucagon in the absence of methylisobutylxanthine (MIX) has no effect on the rate of AIB transport. AIB transport is approx doubled when glucagon is added in the presence of MIX. Calcium depletion and calcium repletion enhance the rate of AIB transport by about 50 and 100%, respectively. Glucagon and N6,O2-dibutyryl cyclic adenosine 3';5'-monophosphate (1 x 10(-4) M) further increase the rate of AIB transport by 10% in calcium-depleted cultures and by 50% in calcium-repleted cultures. The stimulation of AIB transport by glucagon as well as by the ionophore can be blocked by the simultaneous addition of cycloheximide (0.1 mM) or actinomycin D (3.2 uM). In the absence of MIX, there is about a two-fold increase in the level of cAMP in response to glucagon. In the presence of MIX, glucagon causes more than 100-fold increase in the level of cAMP. The presence or absence of calcium does not affect the basal or glucagon-stimulated production of cAMP in these cultures. We have reported previously that, in monolayer cultures of rat hepatocytes, calcium repletion enhanced the glucagon stimulation of AIB transport while it markedly inhibited the production of cAMP in response to glucagon. It is suggested that calcium rather than cAMP has a direct effect on the amino acid transport system. (Author abstract) (24 Refs)

24. GENETICS AND BREAST CANCER.

Lynch HT
Dept. Preventive Medicine, Creighton Univ. Sch. Medicine, Omaha, NE
Genetics and Breast Cancer. New York, Van Nostrand Reinhold Company, 253 pp., 1981.

The etiologic role of genetic factors in breast cancer (BC) are discussed with regard to epidemiology, biostatistics, genetics, pathology, and endocrinology. In addition, programs for counseling, surveillance, and management of hereditary BC patients and high-risk individuals are presented in context with site-specific BC pedigrees as well as those that reflect differing patterns of familial tumor associations such as breast/ovarian cancer syndromes. Practical technics are described to help identify patients genetically prone to BC. The risks of birth control pills, other pharmaceuticals, and radiation (as in xeromammography), are, where appropriate, compared with evidence at the infrahuman level. Hormonal studies contrasting high genetic risk with low genetic risk patients are described. Other topics covered include genetic determinants of BC susceptibility, a statistical model for the study of familial BC, pathologic aspects, patient and family management of familial BC, genetic heterogeneity hormones, and purposes, technics, and procedures relating to particular types of breast surgery. (578 Refs)

25. HYPERCALCEMIA IN HEAD AND NECK CARCINOMA: INCIDENCE, ETIOLOGY, AND PROGNOSIS (MEETING ABSTRACT).

Won C, Decker DA, Drelichman A, Al-Sarraf M, Reed ML
Wayne State University, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:602 1982

A retrospective review of all head and neck cancers seen between January 1, 1975 and September 1, 1981 at Harper-Grace Hospital was performed. Of 1438 head and neck cancers, 41 had hypercalcemia during the course of their disease. Ages ranged from 17-80 years, mean 56 years. The incidence of hypercalcemia by site was 13/351 larynx, 7/280 pharynx, 19/733 oral cavity (floor of mouth 4/171, tongue 9/209, tonsil 5/176, palate 1/95, other 0/82), 2/26 nasal cavity, 0/48 salivary gland carcinomas. Of the 41 patients with hypercalcemia, 40 had squamous cell carcinomas (SCC) and one undifferentiated carcinoma. Of the SCC, 9 were poorly differentiated, 15 moderately differentiated, 4 well differentiated, and 12 not specified. Time from diagnosis of cancer to first diagnosis of hypercalcemia ranged from 0-1440 days, mean 191 days. Thirty-seven had Stage IV and four Stage III. Chest radiographs were positive for mass lesions in 17/41. Bone scans of metastatic bone surveys were positive in 13/41, negative in 16/41, and not evaluable in 12. Five had serum PTH (parathyroid hormone) level performed and in all five the PTH level was inappropriately elevated for the serum calcium level, suggesting ectopic PTH production. The hypercalcemia was medically treated in 29/41, successfully with a return to normal calcemia levels in 17/29. Twelve patients received only palliative care. Survival from the first diagnosis of hypercalcemia ranged from 1-514 plus days, mean 80 days, median 33 days. (no Refs)

26. INFLUENCE OF DES (DIETHYLSTILBESTROL), ESTRADIOL, PROTEIN LEVEL AND DIETARY AFLATOXIN (AFB1) ON AFLATOXIN-PROTEIN INTERACTIONS IN RAT LIVER AND KIDNEY CYTOSOLS (MEETING ABSTRACT).

Mainigi KD
Division of Nutritional Sciences, Cornell University, Ithaca, NY, 14853
Proc Am Assoc Cancer Res; 23:913 1982

In order to examine the effects of various risk-modifying factors on carcinogen binding, this study determined the kinds and amounts of aflatoxin-protein complexes formed in target (liver) and nontarget (kidney) organs. Groups of adult male F-344 rats were fed 5 and 20% casein (5C,20C) diets for 14 days. Three hr prior to sacrifice each rat received a single intragastric dose of 130 ng of 3H-AFB1/100 body weight (Bw). In addition, two hr prior to sacrifice, steroid groups received an intraperitoneal dose of (7.5 mg/100 gbw) of DES, or estradiol. Radioactive cytosols were resolved into multiple protein components according to size by Sephacryl S-200 superfine gel. In 20C control profiles, radioactivity was complexed at all molecular levels. Low protein under all dietary treatments caused a drastic to complete (zero to 80%) depletion of radioactivity from molecular species above 160,000 daltons. Its effect on 40 to 160 K regions was changed by AFB1 or estrogens. 20C-estradiol combination led to a very significant reduction in all molecular species above 40K daltons. 20C-DES combination caused a 568% accumulation of toxin in 70 to 160 K regions. All zones combined, DES increased binding by 165%. 20C kidney cytosol had only 48% of the 20C liver activity, which stood only at 25% level above 70 K zones. (no Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Al-Sarraf M.	25
Anderson D.	4
Barrett JC.	18
Bhathal PS.	5
Boyd JA.	14
Branham WS.	17
Brown RW.	5
Brzezinski A.	2
Casagrande JT.	6
Chen L.	12
Costlow ME.	12
Costlow ME.	8
DaGue BB.	11
Dahl GV.	12
Decker DA.	25
Degen GH.	18
Dimarco PE.	1
Drelichman A.	25
Dukes MN.	22
Eling TE.	14
Elis J.	22
Feenstra A.	9
Frederick CB.	17
Grobstein N.	1
Hample A.	8
Heath JE.	17
Henderson BE.	6
Herbst AL.	4
Hildreth NG.	13
Hubby MM.	4
Ird EA.	19
Johnston GA.	4
Kelley DS.	23
Levitt JW.	1
Li JJ.	10
Li SA.	10
Lie TS.	3
Liehr JG.	11
Lynch HT.	24
Mainigi KD.	26
Malejka-Giganti.	10
Martin FI.	5
Matsuzawa A.	20
McGrath CM.	15
McLachlan JA.	18
Meehan C.	5
Miller FW.	1
Murphy SB.	12
Najem GR.	1
Nolten GM.	9
Pike MC.	6
Pui CH.	12
Reed ML.	25
Reiffers S.	9
Roellke SE.	1
Ross RK.	6
Rush BF.	1
Ryan KJ.	21
Schenker JG.	2
Sheehan DM.	17
Smirnova IO.	19
Soule HD.	15
Toh YC.	16
Vaalburg W.	9
Woldring MG.	9
Won C.	25
Wong A.	18
Yamamoto T.	20
Zúmoff B.	7

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Haugen A, Harris C
Div. Cancer Cause and Prevention, NCI, Bethesda, MD
Recent Results Cancer Res; 82:32-42 1982

2. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.

Brzezinski A, Schenker JG
Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
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3. LIVER DISEASES DUE TO HORMONAL CONTRACEPTIVES.

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4. THE WORK OF THE NRPB 1977/80 AND A REVIEW OF THE FIRST 10 YEARS.

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DIETARY FACTORS IN CARCINOGENESIS

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EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

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10. AIR POLLUTION AND CANCER. A REVIEW OF EXPERIMENTAL INVESTIGATIONS.

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METHODOLOGY IN CARCINOGENESIS RESEARCH

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Mutat Res; 98(3):377-387 1982

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Environmental Mutagen Information Center, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
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24. AN EVALUATION OF THE HOST-MEDIATED ASSAY AND BODY FLUID ANALYSIS. A REPORT OF THE U.S. ENVIRONMENTAL PROTECTION AGENCY GENE-TOX PROGRAM.

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25. THE PHYSIOLOGICAL IMPORTANCE OF THE COLONIC MICROFLORA.

Gustafsson BE
Dept. Germfree Res., Karolinska Inst., Box 60 400, S-104 01 Stockholm, Sweden
Scand J Gastroenterol [Suppl]; 17(77):117-131 1982

26. AN ASSESSMENT OF THE ROLE OF MICRODOSIMETRY IN RADIOBIOLOGY.

Goodhead DT
Medical Res. Council Radiobiology Unit, Harwell, Didcot OX11 0RD, England
Radiat Res; 91(1):45-76 1982

OTHER REVIEWS IN CARCINOGENESIS

27. PSYCHOSOCIAL ASPECTS OF CANCER.

Cohen J, Cullen JW, Martin LR
Sch. Social Welfare, Univ. California, Los Angeles, Los Angeles, CA
Psychosocial Aspects of Cancer. New York, Raven Press, 320 pp., 1982.

☆ U.S. GOVERNMENT PRINTING OFFICE: 1982-381-847:204

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HORMONAL CARCINOGENESIS

SERIES CK05 No. 82/12

DECEMBER, 1982

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In this issue:

- **ORAL CONTRACEPTIVES AND HUMAN CANCER** 1-4
- **ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER** 5
- **MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES** 6-8
- **HORMONAL CARCINOGENESIS IN ANIMALS** 9-13
- **REVIEWS AND OTHER RELATED STUDIES** 14-18

ORAL CONTRACEPTIVES AND HUMAN CANCER

1. ORAL CONTRACEPTIVE STEROIDS AND MALIGNANCY.

Grant E
No affiliation given
Clin Oncol; 8(2):97-102 1982

Current literature data on the cancer incidence among the users of oral contraceptive steroids (OCS) are reviewed. The use of OCS was shown to be associated with considerable increase of the incidence of breast cancer and cervical cancer. The largest increase in the incidence of breast and cervical cancer was observed in women 15-24 yr old who have a risk of double exposure to exogenous hormones. (29 Refs)

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2. INCIDENCE AND PREVALENCE OF PRECLINICAL CARCINOMA OF CERVIX IN A BRITISH POPULATION.

Parkin DM, Hodgson P, Clayden AD

International Agency for Res. on Cancer, 150 cours Albert Thomas, 69372 Lyon, France

Br J Obstet Gynaecol; 89(7):564-570 1982

Incidence and prevalence of preclinical carcinoma of the cervix was studied in a random 10% sample of all 97,250 cytology tests carried out in 1976 and 1977 on resident women, and on a separate 40% sample of 2,848 smears which showed cytological abnormality. Prevalence of disease of women receiving their first examination was relatively low, perhaps because by that time, less than a quarter of examinations performed were first tests. Results on prevalence (number and rate/1,000 tests, respectively) for confirmed dysplasia were 145 and 6.2; for confirmed carcinoma in situ, 48 and 2.1; and confirmed microinvasive carcinoma, 51 and 2.2. Results for incidence of disease (number and rate/1,000 person-yr, respectively) for confirmed dysplasia were 287 and 1.98; for confirmed carcinoma in situ, 86 and 0.59; and for microinvasive carcinoma, 53 and 0.36. The crude incidence for all preclinical carcinoma was 3.5/1,000 person-yr. While the data are not complete enough to calculate the person-years at risk for rates in subgroups of the population, the present results suggest that women of widowed/divorced marital status, increasing gravidity, with gynecological symptoms and using contraceptives, are at increased risk of developing this disease. (22 Refs)

3. INCREASED ANDROGENIC ACTIVITY IN WELL-DIFFERENTIATED ENDOMETRIAL ADENOCARCINOMA.

Grattarola R

Ottava Strada 32, 20090 Milano Sifelice, Italy

Gynecol Oncol; 14(1):40-48 1982

Well-differentiated adenocarcinoma of the endometrium was diagnosed in three patients with polycystic ovary syndrome (PCO) and in two long-term users of an oral contraceptive (ethinylestradiol plus dimethisterone), all five at premenopausal age (from 28 to 36 yr). These patients had high urinary testosterone. None underwent hysterectomy; the three with PCO were treated by wedge resection of the ovaries, and the two oral contraceptive users by simple curettage and discontinuation of oral contraception. The treatment was able to revert the endometrial pattern to normal as well as decrease the urinary level of testosterone. These patients were followed up for 3 to 10 yr since the hormonal study and none has so far had a recurrence. The testosterone excretion level was determined in an additional 26 patients with well-differentiated adenocarcinoma and in 14 with undifferentiated adenocarcinoma of the endometrium. It was found that the testosterone excretion level was significantly increased in patients with well-differentiated adenocarcinoma but not in patients with undifferentiated adenocarcinoma of the endometrium. (Author abstract) (18 Refs)

4. THE ASSOCIATION OF PRIMARY HEPATOCELLULAR CARCINOMA (PHC) WITH HBSAG POSITIVITY IN ASIAN PATIENTS ON HORMONAL CONTRACEPTIVE AGENTS IN SINGAPORE (MEETING ABSTRACT).

Oon CJ, Tsakok M, Singh R

University Department of Medicine, Singapore General Hospital, Singapore, Singapore

Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver, February 7-12, 1982, Kowloon, Hong Kong. Asian Pacific Association for the Study of the Liver and International Association for the Study of the Liver 110 pp., 1982.

Between 1979 and 1981 an ongoing prospective study was made on 236 female individuals on hormonal contraceptive agents (HCA). The objective was to determine the relationship between HCA and incidence of PHC in HCA takers and non-takers in an environment where the natural hepatitis B carrier rate in adult asymptomatic females was about 8% (by radioimmunoassay). Patients' sera were tested for alpha-fetoprotein (AFP) by CIE which in our laboratories has a detection limit of 80 ng/ml. Other tests included alpha 1 antitrypsin, Hepatitis B surface antigen (AUSRIA-II), anti-Hepatitis B core (anti-HBc) antigen (CORAB). The age group of study was 21-51 yrs, median 32 yrs; 3/236 (1.3%) HCA had PHC. These were 3 Chinese women between the ages of 26-29 yrs. The overall annual age specific incidence rates for PHC in Singapore for females aged 25-29 yrs is 0.172 per 100,000. Also 1,000 matched females non-HCA group showed no evidence of PHC over this period of study. Twenty-four HCA patients were HBsAg positive. All 3 PHC patients (13%) were HBsAg, anti-HBc positive. No PHC were seen in the other races - Malays (16), Indians (11) and others (3). One hundred and twelve of 236 (48%) were anti-HBc positive. The HCA taken were Nordette 85, Microgynon 14, Eugynon 36, Neogynon 26, Ovral 26, Gynovlar 6, Ovalen 2, Anovlar 10, New Lyndiol 10, Norethisterone 1, Lyndiol 1, Depoprovera 3. Ovral, Anovlar, Gynovlar and Ovalen were the HCA used by the PHC patients. Chinese females who are HBsAg positive appear to be at higher risk of having PHC than HBsAg negative females on HCA. (no Refs)

ROLE OF HORMONES IN THE ETIOLOGY OF HUMAN CANCER

5. EPIDEMIOLOGY OF BREAST CANCER.

Marchant DJ

Tufts-New England Medical Center, Boston, MA

Clin Obstet Gynecol; 25(2):387-392 1982

The incidence of breast cancer (BC) and risks associated with BC are discussed. A number of factors have been associated with increased risk for BC including demographic, anthropometric, dietary, menstrual, reproductive, hormonal, genetic, and others, including a history of benign breast disease. Key risk factors include previous cancer of one breast, age, age at menarche, age at full-term pregnancy, age at menopause, and wt. The woman with previous cancer of one breast is at risk for cancer in the opposite breast. Studies indicate that the risk is approx 1% per yr. Evidence suggesting that estrogens play an important part in determining the hormonal milieu that favors the development of human BC exists. Risk factors noted in epidemiologic studies are associated with changes in the production of estrogen. Height and wt factors that contribute to increased risk in postmenopausal women can be explained by increased peripheral conversion of androgen to estrogen. The administration of estrogens to postmenopausal women may result in a small increase in the risk of BC. Growth rate of human malignant BC cells in tissue culture is enhanced by estrogens in physiologic concentration. Therapeutic strategies that are effective in the treatment of BC in premenopausal women can be explained on the basis of reduction or elimination of endogenous estrogens. Recent studies on the mechanism of action of estriol indicate that it is neither an impeded estrogen nor an estrogen antagonist when present in continuous of chronic fashion. Most investigators suggest that estrogen is preparative rather than carcinogenic. One of the risk factors that is alterable is obesity, particularly in the postmenopausal woman. (14 Refs)

MECHANISMS OF HORMONAL CARCINOGENESIS: HORMONE RECEPTOR STUDIES

6. BIO-CLINICAL PROBLEMS IN THE SCREENING OF BREAST CANCER.

Toma S, Serra GE, Raffanti S, Canavese G, Margarino G, Massa T, Santi L
Scientific Inst. Study Treatment Cancer, Genoa, Italy
Acta Thermogr; 6(1-3):71-73 1981

Correlations between histologic grading, hormone receptor concentration, and contact thermographic (CT) findings were investigated in 780 women with suspected breast lesions. Eighty-four patients had breast cancer. Problems affecting the accuracy of breast cancer screening are discussed. Pre-selection of screened women, based on a cumulative risk factor less than 60, reduced to 50% the population screened yet identified 76% of the breast cancers present in the whole population. In the present series, a predictable value of 40% was obtained for CT. No significant correlation between CT features and both histological grade and hormone receptor concentration in breast tumors was observed. The harmless nature, low cost and relative reliability of CT recommend its use in the screening of young high-risk women who require repeated check-up. (8 Refs)

7. DESIGN, SYNTHESIS AND BIOLOGICAL PROPERTIES OF ESTROGEN RECEPTOR BINDING BREAST TUMOR LOCALIZING AGENTS.

Senderoff SG
University of Illinois at Urbana-Champaign, Urbana, IL
Diss Abstr Int [B]; 42(9):3696-B 1982

Several steroidal estrogens halogenated on the D-ring were synthesized and subjected to preliminary in vitro evaluation for usefulness as estrogen receptor binding radiopharmaceuticals. Two of these compounds, 16 alpha-bromoestradiol-17beta and 11 beta-methoxy-16-alpha-bromoestradiol-17beta exhibited high binding affinity for the estrogen receptor, and were chosen for development into radiopharmaceuticals with the potential to act as breast tumor localizing agents. They were used to image DMBA induced mammary adenocarcinoma in mature female rats with the use of the Anger scintillation camera. [77Br]-16 alpha-Bromoestradiol-17 beta was further evaluated (dosimetry, pharmacology) for use as scintigraphic agent in humans. This compound was used to obtain an image of a primary human breast tumor that was shown to contain high levels of estrogen receptor upon removal. These results are the first example of scintigraphic imaging of estrogen receptor containing mammary tumors in animals or humans utilizing a receptor binding radiopharmaceutical. (no Refs)

8. ARE RECEPTORS TO BILE ACIDS PRESENT IN HUMAN COLORECTAL CANCER? (MEETING ABSTRACT).

Summerton J, Flynn M, Cooke T, Taylor I
University of Surgical Unit, Southampton University Medical School, Southampton General Hospital, Southampton, England
British Association of Surgical Oncology Summer Meeting, July 15-16, 1982, Portsmouth, England British Association of Surgical Oncology; 1982

Although studies have identified bile acids as a probable etiological factor in the development of colorectal cancer the exact nature of this involvement is unclear. A preliminary investigation has been performed to determine whether receptors specific to secondary bile acids (deoxycholic acid) exist in colorectal cancer tissue. Forty-three samples of human colorectal cancer removed at laparotomy and 33 samples of adjacent colon were studied. Bile acid receptor status was analyzed by a modified estrogen receptor method using 14C-deoxycholic acid. Samples of normal stomach and gastric cancer were assayed in an identical manner. Twenty-five point 6 percent of colorectal cancers had specific receptors to deoxycholic acid. They were not identified in benign colorectal tumors or gastric malignancy. Only 1 sample of normal colon contained receptors (p less than 0.01). Metastatic colorectal cancer did not possess specific receptors (5 patients). Further studies have been performed to confirm the specificity of deoxycholic binding. Autoradiographs using 3H-deoxycholic acid demonstrated specific labelling and Scatchard analyses have been performed. In conclusion initial studies have demonstrated specific receptors to deoxycholic acid in human colorectal cancer. It is possible that this binding influences the development and growth of large bowel cancer. (2 Refs)

HORMONAL CARCINOGENESIS IN ANIMALS

9. PROLIFERATIVE LIVER LESIONS AND SEX STEROIDS IN RATS (MEETING ABSTRACT).

Schuppler J, Schulte-Herman R, Gunzel P
No affiliation given
International Symposium of the Society of Toxicologic Pathologists: Rodent Liver Nodules Significance to Human Cancer Risk? May 10-12, 1982, Reston, Virginia. Society of Toxicologic Pathologists 30 pp., 1982.

The steroids which increase the incidence of proliferative liver lesions (PLL) have not been shown to have the characteristics usually associated with classical hepatocarcinogens such as diethylnitrosamine. Therefore, another mechanism must be assumed. A possible explanation is given by the ability demonstrated for a few steroids to promote preneoplastic islands induced by diethylnitrosamine, resulting in an increase in tumor incidence over rats given only the carcinogen. Spontaneous preneoplastic islands in rats occur in various incidences in different strains and we have recently shown that their reaction to steroids enhanced proliferation is the same as the effect on preneoplastic islands produced by classic carcinogens. Sex steroids also enhance the growth of normal hepatocytes. It, therefore, seems reasonable to assume that sex steroids produce

PLLs by acting on spontaneous preneoplastic lesions and not by the mechanisms usually associated with classic carcinogens. Extrapolating the incidence of PLLs in rats to a risk in humans may be highly misleading because of different pharmacokinetic patterns. Even in rats treated orally for two years with sex steroids dosed as multiples of the human contraceptive dose, resorption and bioavailability may vary by a factor of 10 or more. It is therefore inappropriate to state that one sex steroid is more active in the production of PLLs than another, unless the data from pharmacokinetic studies are taken into account. In summary, available evidence shows that sex steroids act as tumor promotors and enhance the growth of normal hepatocytes. It is extremely doubtful whether a sex steroid producing PLLs in the rat after two years of oral treatment can be classified as an initiating tumorigen for the rat and, because of the high incidence of spontaneous preneoplastic lesions in rats, whether any substantial risk for humans can be inferred. (no Refs)

10. LACK OF HEPATOGENOTOXICITY OF ORAL CONTRACEPTIVE STEROIDS.

Yager JD, Fifield DS
Dept. Environmental Medicine, New York Univ. Medical School, 550 First Ave., New York, NY, 10016
Carcinogenesis; 3(6):625-628 1982

The objective of the present study was to determine whether mestranol could initiate hepatocarcinogenesis and whether various gonadal steroids have detectable hepatogenotoxic potential. To test for initiation potential, female, Sprague-Dawley rats were partially hepatectomized and intubated with mestranol (100 or 500 mg/kg) 24 hr later. Twenty-four hr after treatment all rats were transferred to diet containing 0.05% phenobarbital to promote hepatocytes initiated by mestranol treatment. Four mo later an analysis of putative preneoplastic gamma glutamyl transpeptidase positive foci indicated that mestranol did not cause a significant increase in the number of such foci. Hepatogenotoxicity was assessed in two ways, first using alkaline elution to detect liver DNA damage after in vivo treatment with mestranol, and second by detection of DNA repair synthesis in primary cultures of hepatocytes treated with various oral contraceptive steroids. The results of both studies were negative. In conclusion, the oral contraceptive steroids do not exhibit strong initiating or genotoxic potential. (Author abstract) (21 Refs)

11. ENDOCERVICAL CHANGES IN THE GUINEA PIG AFTER TREATMENT WITH 17-BETA-ESTRADIOL AND 9,10-DIMETHYLBENZANTHRACENE.

Thomas JA, Dallenbach FD
Dept. Pathology, St. John's Medical Coll., Bangalore 560034, India
Indian J Med Res; 75:233-244 1982

Administration of 17-beta-estradiol simultaneously with 9,10-dimethylbenzanthracene to young female guinea pigs, produced marked endocervical mucosal hyperplasia. The hyperplasia showed basement membrane thickening, proliferation of basal cells, immature squamous differentiation with mild dysplasia, mucus cell differentiation and combined squamous and mucus cell differentiation. Excessive quantities of mucus were present in the well-differentiated mucus cell. This mucus appeared to be of two morphological types - the electron-dense and electron-lucent type with a fine fibrillar structure. Mucus was seldom seen to be released from these cells. When such release was seen, it was either by single-mucus-globule extrusion or by release of partial - or wholly - membrane bound mucus-globule-packets. The stroma also appeared stimulated. (Author abstract) (9 Refs)

12. HORMONAL FACTORS IN THE INDUCTION OF LEYDIG CELL TUMORS IN MICE.

Healey PK
University of Health Sciences/The Chicago Medical School, Chicago, IL
Diss Abstr Int [B]; 42(10):3965-B 1982

Differences between serum LH (luteinizing hormone), FSH (follicle stimulating hormone) and PRL (prolactin) levels in Leydig Cell tumor (LCT)-sensitive male A/J and LCT-resistant B6/D mice treated with estrogens were examined. The role of ACTH in the development of LCT in cryptorchid male A/J mice was studied. Male mice of the A/J and B6/D strains were treated weekly with 20ug of estradiol benzoate (EB) in corn oil, or a one-time implant of a 10% DES (diethylstilbestrol)-cholesterol pellet starting at one month of age. Serum levels of LH in estrogen-treated animals were reduced to 1 ng/ml or less within two months, while levels in the control animals averaged over 2.5 ng/ml for the same time period. Serum FSH levels were reduced during estrogen administration, while serum PRL levels increased in DES-treated animals over control. Testes weights decreased in both strains during the first eight months of estrogen treatment, thereafter increasing in the A/J mice but not in the B6/D mice. While increases in testes weights correlated with gross tumor development. LC atrophy followed by hypertrophy and hyperplasia appeared often as early as three months of treatment. LCT development in estrogen-treated A/J mice occurred during a decline in serum LH and FSH levels, and an elevation in serum PRL levels. Surgically cryptorchid LCT-sensitive male A/J mice were treated weekly with 24U of ACTHAR in Gelatin, or a 10% DES-cholesterol pellet implant, or both ACTH and DES. Five out of eighteen ACTH-treated animals developed hyperplastic foci of abnormally-appearing Leydig Cells, while gel-treated controls were normal. Seventeen out of ninteen DES-treated animals developed hyperplastic foci of LC while cholesterol pellet controls foci of LC did not appear. All of thirty ACTH/DES-treated animals developed hyperplastic foci, while all control animals were normal. (no Refs)

13. INDUCTION OF A NEW CLASS OF ESTROGEN-DEPENDENT MESENCHYMAL TUMORS IN RABBITS (MEETING ABSTRACT).

Galt RM, Coogan PS, Laing GH, Newton JJ, Hass GM
Rush University, Chicago, IL, 60612
Fed Proc; 41(3):330 1982

One hundred and fifty-six young virgin female (F) and male (M) albino rabbits, divided into groups, were placed on regimens, permuting the following urogenital tumorigenic factors: 240 mg% dietary 2-AAF (2-acetylaminofluorene); gonadectomy (G); 25 mg pellet sc of 17 beta estradiol (Progynon) (E2); 25 or 50 mg im weekly of medroxyprogesterone (Depo-Provera) (P). Pathologic studies showed frequently unique benign multicentric neoplasms of the spleen, kidneys and liver with occasional malignant transformation of those in the spleen. Though there was no proof of common histogenesis, all were composed of large clear pleomorphic undifferentiated mesenchymal cells, productive of a loose glycoprotein-rich intercellular matrix. Tumors occurred at random in spleen and liver but only distally in medullary renal pyramids. Induction required E2 though malignant transformation also required 2-AF, two factors favorable for induction of urogenital tumors. However, occurrence of urogenital tumors was eliminated by the best regimens for induction of the extra-urogenital neoplasms; namely, combinations of 2-AAF, E2 and P. For example, among 16 F and 10 M on these regimens for 21-69 weeks, 20 had splenic tumors of which 7 were malignant, 6 had renal tumors and 2 had liver tumors. Therefore, progesterone was the principal mediator of high incidence of these unique estrogen-dependent mesenchymal tumors in spleen, liver and kidneys of rabbits. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

14. EPIDEMIOLOGY OF CANCER OF THE ENDOMETRIUM.

Mahboubi E, Eyler N, Wynder EL
Mahoney Inst. for Health Maintenance, American Health Foundation, New York, NY
Clin Obstet Gynecol; 25(1):5-17 1982

Epidemiology of endometrial cancer is reviewed, with particular emphasis on preventive approaches utilized by the physician and patient. An increase in endometrial carcinoma incidence has been reported along with a decrease in cervical carcinoma incidence. An inverse relationship has been seen with uterine cervix cancer worldwide: where cervical cancer rates are high, endometrial cancer rates are low, and vice versa. The country with the highest incidence of corpus cancer, including endometrial cancer, is the United States, which also has the highest level of fat consumption, while Japan, with the lowest fat consumption level, has the lowest incidence of corpus cancer. The peak age of endometrial cancer in the United States is approx 10-15 yr after the av age of menopause. The incidence in white women in the United States is almost twice that in black women and is higher than in other nonwhite groups. Nonwhite rates have not exhibited the dramatic rise in incidence that has been observed in white women. The incidence of endometrial cancer increased by 34-75% between 1969 and 1973. Etiologic factors may include hormones, obesity, diabetes mellitus, hypertension, and familial disposition. Some of the proposed etiologic factors require substantiation before being regarded as significant. Obese women and those with heightened estrogenic stimulation reflected by heavy menstrual flow are at increased risk. Long-term use of postmenopausal hormone replacement therapy, particularly at high doses, should be avoided if possible. (50 Refs)

15. HORMONES AND MEDICATIONS (MEETING ABSTRACT).

Lipsett MB
National Institutes of Health, Bethesda, MD, 20205
American Cancer Society National Conference: The Primary Care Physician and Cancer, June 24-26, 1982, Washington, DC American Cancer Society; :A7 1982

Hormones have been shown experimentally to act as cocarcinogens or promoters, ie, they facilitate the carcinogenic event. In the cases of breast and endometrium, those hormones that facilitate growth may also favor carcinogenesis in the human. There is good epidemiologic evidence of breast and endometrial cancer, the risk increasing with increasing duration of use. Periodic progestin-induced withdrawal will probably mitigate the risk of endometrial cancer after the menopause. Prolactin is the important promoter of mammary cancer in the rat and mouse, but its significance in women is still under study. Intermittently elevated prolactin levels have been noted in some women who subsequently developed breast cancer, but epidemologic studies of women who have received prolactin-releasing drugs such as reserpine and perphenazine have not disclosed increased risk. Diethylstilbestrol is listed as a carcinogen but any estrogen can induce mammary cancer in the rodent or vaginal adenosis in the neonatal mouse (an experimental model of human vaginal adenocarcinoma). (no Refs)

16. RESPONSE OF LIVER FOCI IN RATS TO HEPATIC TUMOR PROMOTERS (MEETING ABSTRACT).

Schulte-Hermann R, Timmermann-Trosiener I, Schuppler J
No affiliation given
International Symposium of the Society of Toxicologic Pathologists: Rodent Liver Nodules Significance to Human Cancer Risk? May 10-12, 1982, Reston, Virginia. Society of Toxicologic Pathologists 30 pp., 1982.

Foci of altered hepatocytes were induced by single doses of initiating hepatocarcinogens and visualized by various histochemical and morphological markers. DNA synthesis, measured by 3H-thymidine and autoradiography, as well as mitotic activity were found to be higher in the foci than in normal hepatocytes; several different tumor promoters (phenobarbital, gestagens, nafenopin, hexachlorocyclohexane) caused further increases in replicative activity of focal cells. Prolonged administration of promoters resulted in appearance of more and larger foci, which exhibited steady growth. Promoter withdrawal led to rapid reductions in size and number of foci. These studies show that the effect of liver tumor promoters is reversible under the conditions employed, as previously noted for skin tumor promoters. Furthermore, promoters seem to encourage growth of a subpopulation of foci that lack mechanisms limiting cell multiplication in normal liver and which depend on the sustained presence of the promoter for survival and/or expression of the specific phenotype of the focal hepatocyte. Finally mechanisms will be considered by which the promoters mentioned as well as other nonmutagenic compounds may produce liver tumors in experimental animals. (no Refs)

17. PLASMA PROLACTIN (PRL) AND ITS METABOLIC CLEARANCE RATE (MCR) IN MALE AND FEMALE RATS FED 5 AND 20% DIETARY FATS (MEETING ABSTRACT).

Clinton SK, Mulloy AL, Visek WJ
University of Illinois, Urbana, IL, 61801
Fed Proc; 41(3):357 1982

It has been proposed that prolactin mediates the enhancement of mammary carcinogenesis by dietary fat. We have studied the effect of dietary fat level (10 and 40% of calories as corn oil) on plasma immunoreactive PRL and its MCR in male and female Sprague-Dawley rats. Rats were assigned to modified AIN diets at weaning. After 10 weeks, 15 rats per treatment were decapitated and trunk blood was assayed for PRL by radioimmunoassay. For the MCR studies 10 male and female rats per diet were anesthetized with pentobarbital, fitted with a jugular cannula and treated with 2-bromo-alpha-9 ergocryptine prior to receiving an exogenous bolus of PRL and collection of sequential blood samples to determine PRL clearance. There was no significant effect of fat on plasma PRL (ng/ml) in females at metestrus-diestrus [23 on low fat (LF) vs 17 on high fat (HF)] or proestrus-estrus [339 (LF) vs 329 (HF)]. There was also no significant difference in plasma PRL in male rats fed LF (39) vs those fed HF (55). Although male rats show a higher MCR than females there was no significant effect of fat. The MCR for males was .80 ml/min on LF and .76 mg/min on HF. The MCR for female rats was .36 and .42 respectively. The PRL and MCR data fail to show that dietary fat significantly changes the plasma PRL levels or its MCR. (no Refs)

18. REDUCED EPIDERMAL GROWTH FACTOR RECEPTORS IN REVERTANTS OF SV40 TRANSFORMED 3T3 CELLS REACQUIRING SERUM DEPENDENCE (MEETING ABSTRACT).

Pollack R, Powers S, Graham GM, Boersig MR, Fisher P
Department of Biology, Columbia University, New York, NY, 10027
Proc Am Assoc Cancer Res; 23:234 1982

Transformation of mouse cells by the DNA tumor virus SV40 results in transformants which display a spectrum of phenotypic alterations, including: serum-independence (S+), anchorage-independence (A+) and tumorigenicity (T+). By employing 5-fluorodeoxyuridine -or bromodeoxyuridine- negative selection it has been possible to develop a series of subclones from an SV40 transformed 3T3 Swiss mouse embryo cell line which exhibit only a partial complement of transformed properties. In the present study we have analyzed a series of such subclones to determine if any of the altered phenotypes correlate with changes in epidermal growth factor (EGF) receptors. The cell types used include: the parental 3T3 cell line (S-A-); SV101, an SV40 transformed 3T3 cell line (S+A+); Agamma4, a revertant of SV101 which is S-A+; LS1, a revertant of SV101 which is S-A-; F1 101, a flat revertant of SV101 which is S+A-; and B8, a mock-revertant of SV101 cells which is S+A+. SV101 cells bound 10 to 20% less 125I-EGF on a per cell basis than did the 3T3 parental cell line. The F1 101 (S+A-) and B8 (S+A+) cell lines bounds equivalent or higher concentrations of 125I-EGF than 3T3 cells. In contrast, Agamma4 (S-A+) and LS1 (S-A-) cells bound only 50% to 33%, respectively, as much EGF as control 3T3 cells. These findings suggest that reversion of SV40 transformed cells back to a serum-dependent phenotype, but not an anchorage-dependent phenotype, is associated with a reduction in cell surface receptors for the polypeptide growth hormone EGF. (no Refs)

AUTHOR INDEX WITH CITATION NUMBERS

Boersig MR 18
Canavese G. 6
Clayden AD 2
Clinton SK 17
Coogan PS 13
Cooke T. 8
Dallenbach FD 11
Eyler N. 14
Fifield DS 10
Fisher P. 18
Flynn M. 8
Galt RM 13
Graham GM 18
Grant E. 1
Grattarola R. 3
Gunzel P. 9
Hass GM 13
Healey PK 12
Hodgson P. 2
Laing GH 13
Lipsett MB 15
Mahboubi E. 14
Marchant DJ 5
Margarino G. 6
Massa T. 6
Mulloy AL 17
Newton JJ 13
Oon CJ 4
Parkin DM 2
Pollack R. 18
Powers S. 18
Raffanti S. 6
Santi L. 6
Schulte-Herman 9
Schulte-Hermann 16
Schuppler J. 16
Schuppler J. 9
Senderoff SG 7
Serra GE 6
Singh R. 4
Summerton J. 8
Taylor I. 8
Thomas JA 11
Timmermann-Tros 16
Toma S. 6
Tsakok M. 4
Visek WJ 17
Wynder EL 14
Yager JD 10

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. CURRENT APPROACHES TO THE EXPERIMENTAL INVESTIGATION OF CHEMICALS IN RELATION TO CANCER OF THE BRAIN.

Swenberg JA, Zimmerman HM, Maltoni C, Kurland L, Laerum OD, Kleihues P, Selikoff I, Heidelberger C
Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709
Ann NY Acad Sci; 381:43-53 1982

2. PRODUCTION OF BRAIN TUMORS WITH AROMATIC HYDROCARBONS.

Zimmerman HM
Montefiore Hosp. and Medical Center, 111 East 210th St., Bronx, NY, 10467
Ann NY Acad Sci; 381:320-324 1982

3. ORAL CONTRACEPTIVE STEROIDS AND MALIGNANCY.

Grant E
No affiliation given
Clin Oncol; 8(2):97-102 1982

4. METAL CARCINOGENESIS - WHAT IS REAL (MEETING ABSTRACT).

Furst A
Institute of Chemical Biology, University of San Francisco, San Francisco, CA, 94117
Environmental Analytical Chemistry, Airborne Mutagens and Carcinogens, June 16-18, 1982, Provo, Utah. Electric Power Research Institute 44 pp., 1982.

5. GENETIC EFFECTS OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE AND ITS HOMOLOGS.

Gichner T, Veleminsky J
Inst. Experimental Botany, Czechoslovak Acad. Sciences, Flemingovo 2, 160 00 Praha 6, Czechoslovakia
Mutat Res; 99(2):129-242 1982

RADIATION CARCINOGENESIS

6. PROBLEMS IN ASSESSING THE CANCER RISKS OF LOW-LEVEL IONIZING RADIATION EXPOSURE. VOLUME 1.

Comptroller General of the United States
(c/o Superintendent of Documents), United States General Accounting Office, Document Handling and Information Services Facility, P.O. Box 6015, Gaithersburg, MD, 20760
Problems in Assessing the Cancer Risks of Low-Level Ionizing Radiation Exposure. Volume 1. Washington, D. C., U. S. General Accounting Office, 85 pp., 1981.

7. PROBLEMS IN ASSESSING THE CANCER RISKS OF LOW-LEVEL IONIZING RADIATION EXPOSURE. VOLUME 2.

Comptroller General of the United States
(c/o Superintendent of Documents), United States General Accounting Office, Document Handling and Information Services, P.O. Box 6015, Gaithersburg, MD, 20760
Problems in Assessing the Cancer Risks of Low-Level Ionizing Radiation Exposure. Volume 2. Washington, D. C., U. S. General Accounting Office, 690 pp., 1981.

8. RISKS OF NUCLEAR ENERGY AND LOW-LEVEL IONIZING RADIATION. REPORT OF AN AMA ADVISORY PANEL TO THE COUNCIL ON SCIENTIFIC AFFAIRS OF THE AMERICAN MEDICAL ASSOCIATION.

Ashare AB, Lave LB, Lincoln TA, Lushbaugh CC, Murray SS, Saenger EL, Schaefer WW, Tupper CJ, Wald N
Dept. Nuclear Medicine, St. Elizabeth's Hosp., Boston, MA
Risks of Nuclear Energy and Low-Level Ionizing Radiation. Report of an AMA Advisory Panel to the Council on Scientific Affairs of the American Medical Association. Monroe, WI, American Medical Association, 40 pp., 1981.

9. ESTIMATION OF RISK OF CANCER INDUCTION IN POPULATIONS EXPOSED TO LOW-LEVEL RADIATION.

Fabrikant JI
Donner Lab., Univ. California, Berkeley, CA, 94720
Invest Radiol; 17(4):342-349 1982

10. EVOLUTION OF THE CONCEPTS AND STANDARDS OF RADIATION PROTECTION.

Xie Z
Inst. Nuclear Energy Academia Sinica, People's Republic of China
Zhonghua Fangsheyixue Yu Fanghu Zazhi; 1(1):2-12 1981
In CHI

11. IONIZING RADIATIONS: DNA DAMAGE, MUTAGENICITY AND MORPHOLOGICAL TRANSFORMATION IN MAMMALIAN CELLS. CARCINOGENICITY IN RODENTS AND IN HUMAN.

Parodi S, Taningher M, Toma S, Scarpati D, Santi L
Dept. Oncology, Genoa Univ., Genoa, Italy
Acta Thermogr; 6(1-3):10-15 1981

DIETARY FACTORS IN CARCINOGENESIS

12. CONTROLLING CADMIUM IN THE HUMAN FOOD CHAIN: A REVIEW AND RATIONALE BASED ON HEALTH EFFECTS.

Ryan JA, Pahren HR, Lucas JB
Municipal Environmental Res. Lab., U.S. Environmental Protection Agency, Cincinnati, OH, 45268
Environ Res; 28(2):251-302 1982

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

13. THE EPIDEMIOLOGY OF CANCER IN CHINA.

Armstrong B
Dept. Medicine, Univ. Western Australia, Queen Elizabeth II Medical Centre, Nedlands, Western Australia, Australia
World Health Forum; 3(1):95-101 1982

14. EPIDEMIOLOGY OF CANCER OF THE ENDOMETRIUM.

Mahboubi E, Eyler N, Wynder EL
Mahoney Inst. for Health Maintenance, American Health Foundation, New York, NY
Clin Obstet Gynecol; 25(1):5-17 1982

15. HOW TO PREVENT CANCER OF STOMACH AND COLON: SMALL MICROBES ARE BIG PRODUCERS OF CARCINOGENS.

Stortebecker P
Akerbyvagen 282, S-183 35 Taby/Stockholm, Sweden
How to Prevent Cancer of Stomach and Colon: Small Microbes are Big Producers of Carcinogens. Stockholm, Stortebecker Foundation for Research, 72 pp., 1981.

16. RELEVANCE OF COLONIC MUCOSAL INFLAMMATION TO AETIOLOGY.

Earnshaw P, Busuttil A, Ferguson A
Gastrointestinal Unit, Univ. Edinburgh, Edinburgh EH4 2XU, England
Recent Results Cancer Res; 83:31-44 1982

17. COLORECTAL CANCER: ETIOLOGY.

Kinlen LJ
Cancer Res. Campaign, Radcliffe Infirmary, Oxford OX2 6HE, England
Recent Results Cancer Res; 83:11-20 1982

18. ACUTE MYELOID LEUKEMIA FOLLOWING TREATMENT OF HODGKIN'S DISEASE. A REVIEW.

Grunwald HW, Rosner F
(c/o Rosner), Queen Hosp. Center Affiliation, Long Island Jewish-Hillside Medical Center, 82-68 164th St., Jamaica, NY, 11432
Cancer; 50(4):676-683 1982

19. PEUTZ-JEGHERS SYNDROME AND BILATERAL BREAST CARCINOMA.

Trau H, Schewach-Millet M, Fisher BK, Tsur H
Dept. Dermatology, Chaim Sheba Medical Center, Tel-Hashomer, Israel
Cancer; 50(4):788-792 1982

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

20. HEALTH EFFECTS OF EXPOSURE TO DIESEL EXHAUST: IMPACTS OF DIESEL-POWERED LIGHT-DUTY VEHICLES.

Griffin HE, Brusick DJ, Castagnoli N, Crump KS, Goldschmidt BM, Higgins IT, Hoffmann D, Horvath SM, Nettesheim P, Stuart BO, Witschi H
Graduate Sch. Public Health, San Diego State Univ., San Diego, CA
Health Effects of Exposure to Diesel Exhaust: Impacts of Diesel-Powered Light-Duty Vehicles. Washington, D. C., National Academy Press, , 169 pp., 1981.)

21. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: THE RUBBER INDUSTRY.

IARC Working Group
Div. Environmental Carcinogenesis, International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum 28: 486 pp., 1982.

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

22. CONCEPTS IN DRUG METABOLISM. PART B.

Jenner P, Testa B
Univ. Dept. Neurology, Inst. Psychiatry, London, England
Concepts in Drug Metabolism. Part B. New York, Marcel Dekker, Inc., Drugs and Pharmaceutical Science, Vol. 10, 627 pp., 1981.

23. CARCINOGENESIS, VASCULAR DISEASE, AND THE FREE RADICAL REACTION.

Johnson FC
Hall House Cottage, The St., Rickinghall, Diss, Norfolk IP22 1EG, England
Nutr Cancer; 3(3):117-121 1982

24. DNA MODIFICATION AND REPAIR IN THE EXPERIMENTAL INDUCTION OF NERVOUS SYSTEM TUMORS BY CHEMICAL CARCINOGENS.

Kleihues P, Patzschke K, Doerjer G
Pathologisches Institut, Albert Str. 19, 78 Freiburg, W. Germany
Ann NY Acad Sci; 381:290-303 1982

25. DNA REPAIR: A LABORATORY MANUAL OF RESEARCH PROCEDURES. VOLUME 1-PART A.

Friedberg EC, Hanawalt PC
Dept. Pathology, Stanford Univ., Stanford, CA
DNA Repair: A Laboratory Manual of Research Procedures. Volume 1 - Part A. New York, Marcel Dekker Inc., 273 pp., 1981.

26. DNA REPAIR: A LABORATORY MANUAL OF RESEARCH PROCEDURES. VOLUME 1-PART B.

Friedberg EC, Hanawalt PC
Dept. Pathology, Stanford Univ., Stanford, CA
DNA Repair: A Laboratory Manual of Research Procedures. Volume 1 - Part B. New York, Marcel Dekker Inc., 360 pp., 1981.

MODIFICATION OF CARCINOGENESIS

27. RETINOIDS AS CHEMOPREVENTIVE AND ANTICANCER AGENTS IN INTACT ANIMALS (REVIEW).

Hill DL, Grubbs CJ
Southern Res. Inst., Box 3307-A, Birmingham, AL, 35255
Anticancer Res; 2(1/2):111-124 1982

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

28. THE CONTRIBUTION OF THE VIRAL THEORY OF TUMOR ORIGIN TO ONCOLOGY.

Mazurenko NP
Center Oncology Res., USSR Acad. Medical Sciences, Moscow, USSR
Vopr Onkol; 28(5):7-12 1982
In RUS

29. PERSPECTIVES ON ENDOGENOUS RETROVIRUSES IN NORMAL AND PATHOLOGICAL GROWTH.

Weiss RA
Inst. Cancer Res., Fulham Road, London SW3 6JB, England
Curr Top Microbiol Immunol; 98:127-132 1982

30. ENDOGENOUS RETROVIRUSES OF MICE AND CHICKENS.

Steffen DL, Robinson H
Worcester Foundation Experimental Biology, 222 Maple Ave., Shrewsbury, MA, 01545
Curr Top Microbiol Immunol; 98:1-10 1982

31. POSSIBLE IMMUNOLOGICAL MECHANISMS IN C-TYPE VIRAL LEUKEMOGENESIS IN MICE.

Ihle JN, Lee JC
Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD
Curr Top Microbiol Immunol; 98:85-101 1982

32. ONCOVIRAL PROTEINS AS CELLULAR ANTIGENS.

Fleissner E, Snyder HW
Memorial Sloan-Kettering Cancer Inst., 1275 York Ave., New York, NY, 10021
Curr Top Microbiol Immunol; 98:37-80 1982

33. GENITAL WARTS: RECENT ADVANCES.

Oriel JD
Dept. Genito-Urinary Medicine, Univ. Coll Hosp., London, England
Clin Exp Dermatol; 7(4):361-367 1982

34. PRIMARY HEPATOCELLULAR CARCINOMA AND HEPATITIS B VIRUS.

Blumberg BS, London WT
Dept. Medicine, Univ. Pennsylvania, Philadelphia, PA
Curr Probl Cancer; 6(12):1-23 1982

35. IMMUNOLOGICAL ASPECTS OF EXPERIMENTAL BRAIN TUMORS. (REVIEW).

Stavrou D, Bilzer T, Hulten M, Zanker KS, Anzil AP, Haglid KG, Dahme E
Dept. Functional Pathology, Univ. Munich, 8 Koniginstr., 8000 Munich 22, W. Germany
Anticancer Res; 2(3):151-155 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

36. MUTAGEN ASSAY WITH ARABIDOPSIS: A REPORT OF THE U. S. ENVIRONMENTAL PROTECTION AGENCY GENE-TOX PROGRAM.

Redei GP
Univ. Missouri, Columbia, MO, 65211
Mutat Res; 99(2):243-255 1982

37. METABOLIC AND MODULATING FACTORS IN TOXICITY AND CHEMICAL CARCINOGENESIS (MEETING ABSTRACT).

Fishbein L

HORMONAL CARCINOGENESIS

National Center for Toxicological Research, Jefferson, AR

1st World Congress on Toxicology and Environmental Health, May 27-30, 1982, Washington, D.C. American College of Toxicology 28 pp., 1982.

38. PROCEEDINGS OF THE INHALATION TOXICOLOGY AND TECHNOLOGY SYMPOSIUM HELD IN KALAMAZOO, MI, 23-24 OCTOBER, 1980.

Leong BK

Industrial Toxicology Lab., Upjohn Co., Kalamazoo, MI, 49001

Proceedings of the Inhalation Toxicology and Technology Symposium held in Kalamazoo, MI, 23-24 October, 1980. Ann Arbor, MI, Ann Arbor Science Publishers, Inc., 313 pp., 1981.

39. CHEMICAL CLASS SEPARATION AND DETAILED IDENTIFICATION OF GENOTOXIC POLYCYCLIC AROMATIC COMPOUNDS IN AIRBORNE PARTICULATES (MEETING ABSTRACT).

Later DW, Lee ML

Department of Chemistry, Brigham Young University, Provo, UT, 84602

Environmental Analytical Chemistry, Airborne Mutagens and Carcinogens, June 16-18, 1982, Provo, Utah. Electric Power Research Institute 44 pp., 1982.

OTHER REVIEWS IN CARCINOGENESIS

40. SPONTANEOUS NEOPLASTIC PATHOLOGY IN CONTROL RATS - A REVIEW.

Nunziata A, Storino AA

Centro Ricerca Farmaceutica, Via Tito Speri, 14 Pomezia, Roma, Italy

Vet Hum Toxicol; 24(4):243-247 1982

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